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DIVISION OF NARCOTIC DRUGS

Geneva

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Table of Contents

	Page
Present state of the coca-leaf habit in Colombia, by Professor Jorge Bejarano...	1
Medical deontology and the reporting of drug addicts, by Professor M. Müller & Dr. P. Müller	7
Hong Kong's prison for drug addicts	13
Manufacture of alkaloids from the poppy plant in Hungary, by Dr. I. Bayer.....	21
Human pharmacology and addictiveness of ethyl 1-(3-Cyano-3,3-phenylpropyl)-4-phenyl-4-piperidine carboxylate hydrochloride (R-1132, Diphenoxylate), by H. F. Fraser & H. Isbell	29

Present state of the coca-leaf habit in Colombia

By Professor Jorge Bejarano,
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Over ten years have elapsed since action was first taken against coca-leaf chewing. The coca habit occurs locally among a few indigenous groups; geographically, it is found in the areas of Colombia where the coca bush has been cultivated. It is the leaves of this bush which are chewed.

It is not necessary to revert in this report to the history of the coca habit, which dates back to the period of Manco Capac, the founder of the powerful Inca tribe which carved out a vast empire. There exists a sufficient body of literature and research on the subject, the chief interest of which resides in its sociological and human aspects. For us, it is evidence of the great ingenuity of man in discovering plants and substances which can provide him with abnormal sensations and in grasping the secret of the chemical processes for the extraction of the necessary elements by which he could produce that state of factitious happiness and euphoria that is generated by drunkenness or the effects of alkaloids.

This absence of a reference to the historical background will, however, be more than compensated if we note the serious concern now being shown by the governments and international organizations which are studying the necessary measures to eradicate a habit that has a demonstrably adverse effect on physical and mental health.

Nor is it necessary for the purposes of this report on the present state of the problem of coca addiction in Colombia to describe once again the mental, psychological, economic, social and pathological phenomena produced by coca addiction, for they have been described so often before with an abundance of detail. The fact that, after centuries, these phenomena are still present is the reason for the campaigns carried out both in Peru and in Colombia by health experts, sociologists and chemists.

What must, however, be repeated whenever the problem of coca addiction is mentioned is that this problem has persisted throughout the centuries, sometimes because of the neglect of governments and sometimes because of the interests of groups which use it as a means of gaining an economic stranglehold over the indigenous population. There is abundant historical evidence of the immoral use made by man of natural vices, or of vices fostered by civilization, to control the work, land and economy of peoples or tribes who are slaves of opium, alcohol, *chicha* or the coca leaf. The Indians first made use of the coca leaf because of its medicinal properties or of its mythological significance but, having come under the influence of its narcotic effects, they sold themselves into slavery for a period of years which has not yet expired; as has been shrewdly observed by Dr. Luis N. Saenz, neither the independence of the American peoples nor the laws enacted in favour of the Indians to this date have freed them from this slavery.

In my socio-historic monograph, *Nuevos Capítulos sobre el Cocaísmo en Colombia* * (New Chapters on Coca Addiction in Colombia), I pointed out that there would appear to be some justification for the cultivation of the coca bush in Bolivia and Peru, where it has become a source of dollar or foreign exchange earnings because there is a foreign market for the coca leaf, which is used in the preparation of cocaine. The same, however, has never been true of Colombia, where the only purpose of this cultivation is to exploit the indigenous labour and economy in the areas where the coca bush survives, and with it the habit of chewing the coca leaf. Coca addiction has made it possible to subject the indigenous populations to exhausting tasks at miserable wages paid in part in rations of coca leaf. Accordingly, in Colombia there are no economic grounds to justify the cultivation of the coca bush, and still less any of the pseudo-scientific grounds which have been put forward in other countries as an apologia for a habit fraught with serious social, pathological and economic consequences.

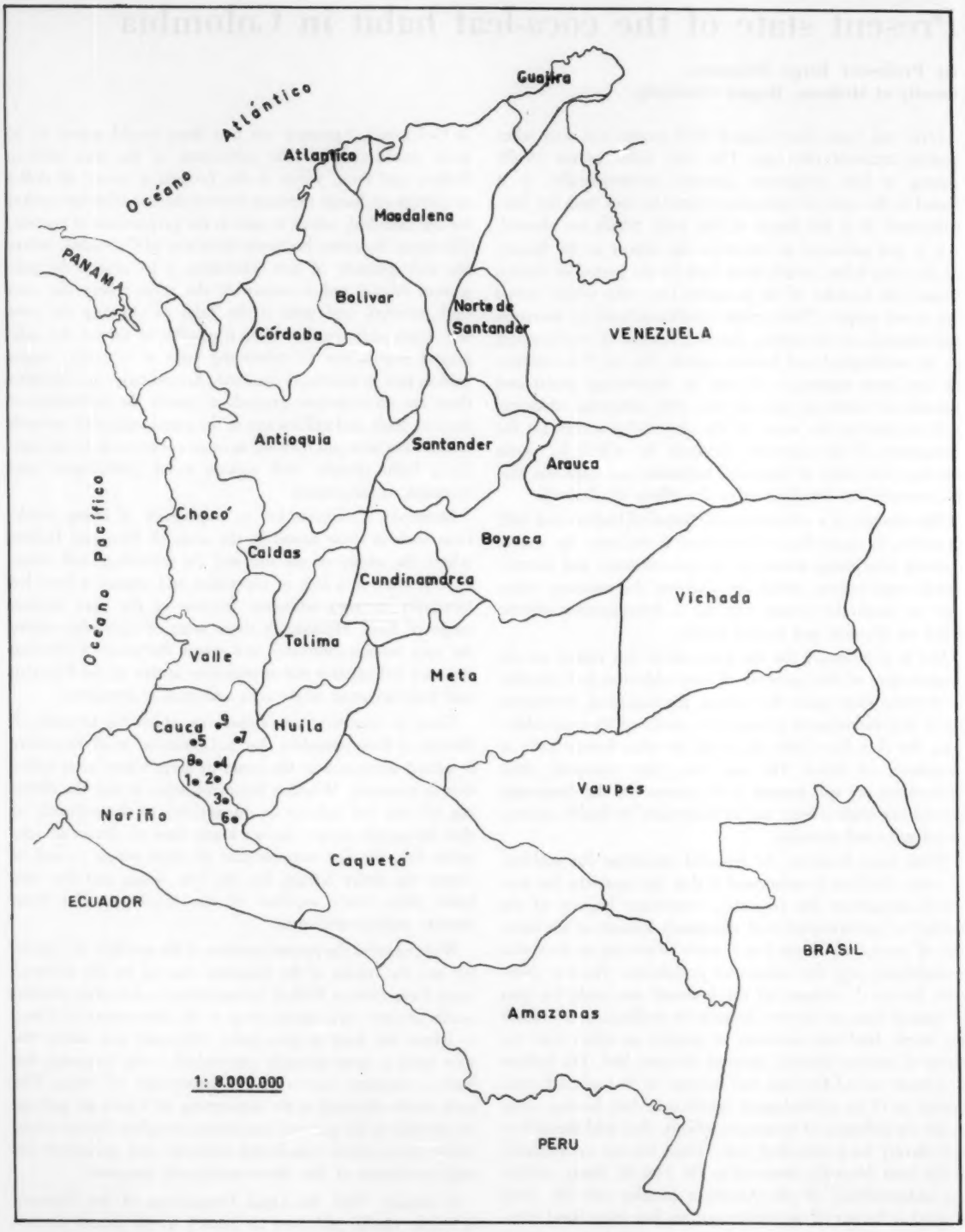
Moreover, Colombia has no experience of living conditions such as those found in the areas of Peru and Bolivia where the aridity of the soil and the prevailing cold winds have resulted in a lack of vegetation and appear to have led inevitably to coca addiction because of the very narrow range of food. Housing in those areas of Colombia where the coca bush is cultivated and where the habit of chewing the coca leaf exists is not as primitive as that of the Peruvian and Bolivian areas where coca addiction is prevalent.

There is, however, one respect in which the situation in Bolivia or Peru resembles that in Colombia: in all three there is a food deficiency in the zones or areas where coca addiction is common. Whether the explanation is that the chewing of coca leaf induces an insensitivity of the stomach, or that the people simply do not know how to obtain an adequate diet, the fact remains that all these people — and of course the entire family, for the low wages and the coca habit affect every member of the family — suffer from chronic undernourishment.

With regard to the present position of the problem in Colombia and the results of the measures enacted by the Government from 1946 to 1948, it is interesting to note that whereas results are not very encouraging in the department of Cauca — where the bush is principally cultivated and where the coca habit is most strongly entrenched — the campaign has been a complete success in the department of Huila. The poor results obtained in the department of Cauca are perhaps attributable to the political conditions prevailing for ten years, which demoralized constituted authority and prevented the implementation of the above-mentioned measures.

In January 1960, the Legal Department of the Ministry of Public Health addressed an inquiry to the sixteen departmental secretaries of public health. Thirteen replied that the

* See *Bulletin on Narcotics*, Vol. IV, No. 3.



MAP OF THE REPUBLIC OF COLOMBIA

MAP OF THE DEPARTMENT OF CAUCA

The department of Cauca

Present population	475,510 inhabitants
Hectares under cultivation	617
Productive trees	500,000
Yearly production	143,650 kg;
Value of the crop	642,000 pesos

Districts where coca is cultivated and consumed

	Number of inhabitants	*Percentage of coca consumers*
1. Bolivar	40,000	20
2. Almaguer	24,500	50
3. San Sebastián	9,300	40
4. La Vega	15,100	35
5. El Tambo	28,500	15
6. Santa Rosa	3,500	20
7. Inza	12,000	15
8. Patia	17,000	5
9. Caldono	13,400	15

coca bush was not cultivated, and the chewing habit did not exist in their territory. One did not reply, and only the two departments of Cauca and Huila reported coca bush cultivation, said to be almost negligible in the latter.

It should be noted that, of the various measures suggested in my study published in 1952, those intended to raise educational, economic, agricultural and housing standards have not been implemented in the campaign against coca addiction.

The Government's measures have now been in force for twelve years; by now, addiction ought to have been completely eradicated, and Colombia ought to be reaping the fruits of a campaign meant to benefit the community and the national economy.

It may be claimed that the chewing habit is now limited to nine municipalities of the department of Cauca, the names of which are given in the attached map together with particulars of the population of each and an estimate (in percentages) of the extent of the coca consumption.

The habit essentially affects the indigenous population; it also affects a very small number of non-indigenous peasants.

The indigenous inhabitants are initiated to the chewing habit at the age of twelve, and maintain it throughout life. Only the indigenous families who are educated and protected by missionaries are free from the habit.

The entire population group affected by the habit works in agriculture, as small-holders or sharecroppers.

Economic conditions for this population group are precarious. Wages vary between 3 and 4 Colombian pesos per day—i.e., 50 or 60 U.S. cents. Housing conditions are deplorable; the inhabitants live in primitive huts with neither drinking water nor sanitation. Those who succeed in becoming coca growers live better, for they can sell the leaf at 2 Colombian pesos per pound—i.e., half a day's wage. In some districts of the department of Cauca, the coca leaf has virtually become currency for the payment of wages; the indigenous inhabitants receive part of their weekly wages in coca leaves, a social malpractice which has been repeatedly reported to the Ministry of Labour.

These wretched conditions perhaps explain the irresistible inclination of the indigenous inhabitants to coca-leaf chewing, by means of which they find, through intoxication, an escape from their loneliness and misery.

In all the municipalities affected by the chewing habit, with the exception of two or three, the health centres suffer from a shortage of personnel and material. One gathers the impression that they ignore the problem of coca addiction.

According to one census, there are 936 coca-bush growers, who cultivate about 617 hectares consisting of 500,000 bushes; the annual production is approximately 143,650 kg, representing a value (at the rate of about 4 pesos per kg) of approximately 600,000 Colombian pesos.

The coca leaf is sold clandestinely in the markets of the growing areas. In addition, there is a clandestine traffic into other municipalities, and even into departments where the habit was thought to have disappeared because the bushes have been destroyed and the sale of the leaf has been brought under control. The departments in question are those of Huila and Narino, bordering on the department of Cauca.

I consider it right to repeat in this report some of the suggestions I have made elsewhere, and to make some additional ones on points which I consider essential to the success of the campaign in Colombia.

(1) The Government of Colombia should ask for expert technical assistance to bring about the necessary changes in agriculture and education in the areas where coca chewing still exists.

(2) The Government should enlist in the campaign the participation of the Ministries of Public Health, Education, Agriculture and Public Works, the Agrarian Bank and the Agricultural Society of Cauca.

(3) By legislation or otherwise, land on which coca is now grown should be exempted from all taxation for five years, on condition that within a period of not more than six months coca must be replaced by fruit, vegetables, leguminous plants, flowers, nursery plants, coffee, sugar cane, soya beans, grass for fodder, or by some other crop which can be used as food for man or beast, or one which enhances the quality of the land (afforestation). It is of course an implication of the benefit of this tax exemption that the public-health, police or civil authorities will have power to destroy plantations which have not been replaced by other crops within six months of the date of the enactment.

(4) The bishops of Popayan and Neiva should be asked to lend the strong support of the clergy to make the campaign a success. In addition, the missionaries who are concerned with the education of the indigenous inhabitants or who employ them in agriculture or cattle breeding should be invited to co-operate.

(5) The Ministry of Labour should station in the coca-growing areas a sufficient number of labour inspectors to discover and punish severely those farmers and employers who pay the weekly wages of their labourers partly in cash and partly in coca leaves. These inspectors should examine the contracts of employment and verify whether they conform with the provisions of the labour legislation.

(6) Pending the replacement of coca by the other crops mentioned above, the Ministry of Public Health, with the co-operation of UNICEF, should carry out an intensive nutrition campaign, issuing milk to children and mothers, and establishing school canteens in the areas in question.

(7) Health centres should be set up in order to carry out an intensive tuberculosis and smallpox vaccination campaign. These centres should instruct the midwives and practitioners whom the indigenous inhabitants consult in the elements of child health and midwifery.

(8) The Rehabilitation Office should be associated with this campaign for the eradication of coca-leaf chewing, and should deal with rural housing in the areas concerned, either by improving existing housing, which fulfils some but not all public health conditions, or by building new houses by any of the methods which have been employed for similar purposes in the areas affected by civil violence.

(9) The co-operation of UNESCO should be enlisted to carry out a programme of education by means of films, pamphlets and booklets in order to cure the present state of ignorance.

Medical deontology and the reporting of drug addicts

By Professor M. Müller & Dr. P. Müller
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1. Man has always sought to escape from his miserable condition into some dream paradise. Like Icarus, we all wish to take off for better lands. This has led to the early discovery of intoxicating substances which procure an artificial paradise. Alcohol, opium and cannabis are certainly among the most used of these substances. Unfortunately, for certain persons, the use of a drug has the effect of establishing a sort of association which renders it increasingly indispensable. Hence the emergence and development of drug addiction, which is now defined as " a state of periodic or chronic intoxication " produced by the repeated consumption of a natural or synthetic drug. The characteristics of drug addiction include: a desire or need to continue taking the drug and obtain it by any means; a tendency to increase the dose; a psychic (or psychological) and generally also a physical dependence on the effects of the drug effects which are detrimental to the individual and to society. This definition, which has been formulated by WHO, adequately sums up the position of drug addicts in relation to their drug and to society. Moreover, it should be remembered that drugs were at first not very numerous; with the development of modern chemistry, however, new products have appeared which have an extremely beneficial action in certain cases, but which can also be the source of new forms of addiction.

2. The manner in which our society has developed has also meant that there is an increasing tendency for persons to seek artificial happiness; there can be no doubt that drug addiction threatens to increase, with a parallel increase in the number of addicts.

3. We are not very well informed regarding the number of drug addicts. A few figures will serve to illustrate this remark. The United Nations report for 1958 indicates that in Brazil the areas having the largest number of drug addicts are the cities of Rio de Janeiro and São Paulo. In Brazil drug addicts are, as a matter of course, committed to a psychiatric hospital. Nevertheless, the total number of addicts under treatment at the psychiatric clinics of São Paulo and Botafogo is nine.

In Canada, it is reported that 3,412 addicts have been numbered, and a census carried out in the United States of America has shown that the number of addicts between 1953 and 1958 was 46,256. In India, opium addicts alone were said to number 432,609. While no doubt considerable differences exist from one country to another, we cannot accept without reservation the statistical information given by some countries. To our mind, drug addiction is a world problem which is on the increase in spite of the steps taken in various directions to deal with it.

The particularly serious character of the problem is shown by a more detailed examination of United States statistics. We have seen that between 1953 and 1958, 46,256 addicts of various kinds were counted. Their break-down into age groups is as follows:

18 – 21	5,550
21 – 30	27,753
30 – 40	8,328
Over 40	4,625

Fifty-nine per cent of these addicts are negroes, and 80% are males. It will be noted that the great majority of drug addicts are between twenty-one and thirty, and that the number of drug addicts who are minors is considerable. In fact, 72% of the total number of addicts in the United States of America are between eighteen and thirty. In the city of New York, however, 60% of drug addicts are less than twenty. It should be added that in Canada, the number of drug addicts aged under twenty was twice as large in 1958 as it was in 1957.

4. We should not lose sight, in this study, of one essential fact: Regardless of whether he is a patient, a former patient, an addict merely indulging in the drug or a doctor, a person who takes drugs will conceal his vice. It is hardly necessary to dwell on the origin of addiction. In our view, there are two groups: that of addicts who first used a drug to quell pain and that of addicts initiated to the drug-taking without any apparent medical reason. For the first group of addicts, medical reasons justified, during a more or less prolonged lapse of time, the use of a beneficial drug; as to the second group, enjoyment alone was sought from the start. The first group consists of occasional addicts who, in principle, appear to be more easily curable; the second group consists of persons who suffer from a veritable psycho-sensorial disease; these persons have constant relapses and tend to become increasingly dependent on the drug. Addicts of the first group will obtain their drugs chiefly by means of medical prescriptions. They will complain of pains which, in their eyes, give them a plausible reason to consult a doctor, or to disturb successive doctors after exhausting the patience or the tacid complicity of one of them. Addicts of the second group, for their part, will resort to *every possible means* of obtaining their drug: illicit purchase; medical prescription obtained on the pretext of a chronic disease; fraud; and even false pretences in all their forms.

Among the addicts of the second group, the young must be considered as being in a special class. Among the young, contagion is easier and the effects of contamination more serious, as the figures show; moreover, their lives will be marked by progressive moral and physical degradation

unless severe remedial measures are taken in time. This new effect of the non-adaptation of youth is a factor of which there is not yet enough awareness in the old world. It is therefore important to stress it.

5. In order to meet this situation, many countries have organized and regulated the purchase, detention and sale of the various addiction-producing substances. Addiction has thus been placed outside the law in these countries and, in consequence, addicts are deemed engaged in unlawful activities. Most narcotic drugs, however, are still much used in medicine, as is the case of opium derivates, for example, and their manufacture and use could not be prohibited altogether. The regulations enacted have therefore been aimed at ensuring that doctors prescribe these substances only to those of their patients who can or will benefit from them. Doctors can come into contact with drug addicts in various ways. In section 4 above, we have seen how attempts may be made to involve doctors as accessories in the use of drugs. This occurs with patients who claim to suffer from painful diseases and, rightly or wrongly, assert that relief is only possible by means of the use of drugs. A doctor may also be consulted by a patient who does not reveal the connexion between his organic disease and his addiction, which he conceals; in this case, the doctor will, by his examination and interrogation of the patient, be able to discern the precise etiology of the latter's condition. Lastly, a psychiatrist or sociologist working in institutions for the observation and readaptation of children will have the opportunity to diagnose cases of drug addiction of more or less long standing among the young persons admitted to the institution.

In certain countries, it has become apparent for some years that if a doctor in the course of his practice could notify these cases of addiction to the judicial or other competent authorities, these authorities would be better equipped in their struggle against addiction.

6. The rule of medical secrecy debars in principle a doctor from disclosing facts which come to his knowledge in the course of his practice; this rule therefore precludes him from notifying cases of addiction.

The rule of medical secrecy is an old concept; it is now much disputed and has come under fire from different quarters concerned with the study of life in society. Life in society appears to be demanding an increasing interference in the private life of individuals by large administrations which regulate their daily life down to the smallest details; it is a paradoxical fact that our societies appear to be progressively moving towards the ideas of Plato's Republic, in which the citizens' lives were directed towards the general welfare.

The question therefore arises whether, in these circumstances, the principle of professional secrecy can still be upheld in absolute and general terms, and whether those things which Hippocrates regarded as sacred and ranked as mysteries can continue to block " social " needs indefinitely.

7. The rule of medical secrecy is based on the requirements of professional ethics and morality, but it has also been incorporated into the laws of various countries. It has even been raised to the status of an international principle by the International Medical Association. In the code of ethics drawn up by that association, which has been accepted by all member countries, the rule of professional secrecy has held a prominent place from the outset.

Actually, the principle of medical secrecy is essentially based on the trust which a patient must be able to place in his doctor. If a patient knows that in certain cases the doctor is entitled to notify his case to the authorities, or even to mention it to other persons, then, if he expects that disclosure to have disagreeable consequences for him, he will prefer to keep his illness secret rather than confide in a doctor. The abolition of medical secrecy, or its relaxation (which would have exactly the same effect) would thus in the long run be harmful to social health.

8. Moreover, as a matter of conscience, a doctor is bound by the trust which is placed in him and, even in the absence of any legislative provision on the subject, he feels very strongly the absolute need not to disclose the information concerned; there can be no doubt that Hippocrates, when he wrote his oath, did no more than codify moral rules known prior to the school of Cos.

9. Lastly, in most countries, the rule of medical secrecy is embodied in legislative provisions which are often very detailed. Jurists are at present seeking to restate the grounds on which these provisions are based. Some believe that the principle of medical secrecy is a matter of public policy, and there can be no doubt that this approach furnishes the easiest, most complete and most satisfactory explanation on the subject. More recently, others have sought an explanation in the existence of a medical contract, a contract originating in the free choice of his physician by the patient; on this basis, a tacit agreement is held to have been reached on a contract by virtue of which the doctor undertakes to place his knowledge and his conscience at the service of his client's health. The fact that the doctor has been freely chosen as a confidant means that whatever the patient confides in him, whether by word of mouth, by allowing the doctor to enter his home, or by permitting him to examine him, must remain secret. It therefore follows that the secret belongs exclusively to the two contracting parties — i.e., the patient and the doctor. There is no possible secrecy between them, and a certificate relating to his illness can always be handed to the patient himself: a doctor cannot invoke medical secrecy in his relations with his patient.

10. Cases, however, often occur in which the patient is not free to select the doctor. The choice of a doctor, instead of being directly made by him, may have been imposed by an administration. The patient may be a minor who does not have full civil capacity, or a mentally deficient person who has lost that capacity; in these cases, there can be no doubt that the secrecy rule remains as binding as ever, although from the legal point of view there can be no question of a contract. Similarly, when the patient dies, the contract is modified, but the secrecy rule persists. It is thus clear that circumstances exist in which the rule of medical secrecy covers a wider field than any contract. Indeed, if the question

is probed deeper, it will be seen that unless the rule of medical secrecy exists, no contract will be possible; the patient confides in the doctor precisely because he knows that the doctor will not betray him. The idea of medical secrecy appears well before any contract is entered into.

11. It is thus apparent that there are many instances in which secrecy goes beyond what would be required in a contract, and covers areas which are a matter solely for a doctor's conscience; in our view, it is therefore appropriate to say that secrecy is here a matter of public policy. There have even been cases in which an obligation has been imposed by law on physicians to notify certain cases, and doctors have refused to comply, considering the orders in question unjust. In France, for example, during the German occupation, doctors were required, whenever they attended a wounded person, to report the fact, giving the person's address and explaining the origin of the wounds. Doctors invariably refused to comply with this requirement, which directly conflicted with the law and regulations in force. Medical secrecy is not only consistent with the nature of things, but transcends all other duties.

12. There are, however, exceptions or departures from the rule in all countries. The operation of social legislation, particularly with regard to industrial accidents and occupational diseases, and the military pension machinery provide everyday examples of such departures. These departures, however, do not effect in any way the trust which the wounded or sick patient has in the doctor. In these cases, the doctor obviously gives medical attention, but acts also — and indeed it could almost be said chiefly — as the agent of the administration which provides " raparation " for the condition affecting the patient; it might be possible to carry the argument even further and to say that the cash idemnity given by the administration concerned is part of the treatment, and results from the action of the doctor.

Another much more serious exception is the notification of contagious diseases. In this case, there can be no doubt that the rule of medical secrecy, in spite of all that we have just said, has had to give way before another rule — also of public policy — the protection of public health.

There has been general agreement that it is essential for cases of contagious diseases to be notified in order to prevent the spread of epidemics.

Moreover, as a general rule, in spite of the unpleasantness involved, patients understand very well the reasons which compel the authorities to make the notification of contagious diseases compulsory. In most cases, compliance with that requirement by the doctor will not lead to any adverse comment by patients.

13. In a growing number of countries there is increasing recognition of the need to treat the drug addict as a patient, and drug addiction as a kind of illness. This does not mean that such an attitude replaces entirely penalties for acts resulting from or related to addiction which violate the laws. But it means that the addict cannot be weaned away from his addiction and rehabilitated in society unless medical, health and social measures are jointly applied. Several countries have advanced well in that direction, and others are commencing to take the first steps. Some of the important measures taken by countries with a view to the control and treatment of an addict as a patient are the obligatory declarations required to be made in respect of addicts by medical practitioners, the registration or licensing of addicts and the compulsory treatment of addicts. In some countries even, all citizens are required to report addicts. The measures taken by countries for the reduction and suppression of addiction are within the framework of the international treaties on narcotic drugs, and particular reference may be made in this connexion to article 15 of the 1931 Convention.

14. In this struggle against drug addiction, the need is apparent to resort to all possible means in order to eradicate this social evil, or at least reduce it in extent, since none of these means by itself can eradicate drug addiction altogether. The control of the manufacture, trade and international traffic in drugs, police measures to check illicit traffic, the control of pharmacies, and the legislation governing the prescription of narcotic drugs have so far proved useful but quite insufficient.

The system introduced on 9 December 1959 in Thailand provides an example of an attempt at a complete system of control and treatment:

(*a*) Abolition of the use of smoking opium and of the sale of opium throughout the country as from 30 June 1959;

(*b*) Notice to opium smokers requiring them to submit an application for registration not later than 31 December 1958;

(*c*) As from 1 January 1959, introduction of a more strict system of control for smoking opium, so as to make it impossible for non-registered drug addicts to use this opium;

(*d*) Abolition of licensed premises for the supply of opium as from 30 June 1959;

(*e*) Establishment of clinics and convalescent centres for opium addicts by the Ministries of Public Health and the Interior;

(*f*) Treatment of drug addicts, whether licensed or not, for six months as from 1 January 1959, and measures connected with the convalescence of these addicts;

(*g*) Enforcement, as from 1 July 1959, of the penalties specified by the legislation on opium against offenders, provision being made for their after-care in a clinic or convalescent home for a period of not more than ninety days upon their release from prison.

On 9 December 1958, the Ministry of Finance issued a notice requiring opium addicts to apply for registration before 31 December 1958, and ordered the owners of premises licensed to issue opium to sell it only to authorized addicts.

No doubt a small additional contribution would be made towards the solution of this grave problem if doctors were required to notify cases of drug addiction. A measure of this kind, however, would not greatly affect the character of the struggle against addiction. Very few cases of drug addiction become known to doctors as a direct result of their ordinary practice. The only cases which they detect in this manner are

those of patients who invoke a painful disease as an excuse for using a drug, and endeavour to obtain prescriptions to procure it from a pharmacy. In their case, however, a notification by the doctor would be quite unnecessary. These cases are soon apparent to the authorities because of the numerous prescriptions, the large number of doctors consulted, the progressive increase in the doses, all of which can be traced by the operation of legislation along the lines of the French law on the prescription and issue of substances included in schedule B. Since the prescriptions are issued in the name of the patients, they constitute in fact compulsory notifications. The majority of drug addicts, however, are unknown to the doctors. This is particularly true of the most dangerous addicts — i.e., those whose addiction is not of pathological origin and who are active in propagating addiction; these addicts obtain their drugs by illicit means. Equally dangerous are those persons who live on the drug traffic and the profits derived from it, and who may or may not be addicts themselves.

In our view, the latter category of addict is the most dangerous and the most numerous. There is no comparison between the number of these addicts and the few isolated cases which may become known to doctors in the course of their practice.

We have cited above some alarming statistical figures in section 3 and, in section 5, we have mentioned the cases in which a doctor in charge of a social service can contribute to the detection of addicts, particularly minors and adolescents.

15. It is, however, possible to classify into two groups those addicts who resort to doctors: the first group includes those who come to a doctor for treatment, asking help to overcome addiction.

These cases are of great interest to a doctor. The patients concerned are certainly entitled to secrecy, provided that the doctor takes a personal interest in their treatment and its results, and endeavours to entrust the patient to a medico-social institution for after-care. There can be no doubt that in no event must the doctor notify these cases.

The second group is that of addicts who consult an unknown doctor purely in search of a prescription which will serve to obtain by licit means the drugs which they need, or which they are unable to obtain by the usual illicit means. These persons cannot be regarded as patients; nor are they mental cases. They consult a doctor purely because of the power he has to issue prescriptions; they are law-breakers who are more or less openly seeking the willing or unwilling complicity of a doctor.

In the case of this group of drug addicts, and this group alone, a doctor would not appear to be absolutely bound by the normal rules of professional secrecy; it would seem that, in these cases, the doctor can make a notification without that implying, strictly speaking, any conflict with medical ethics.

Lastly, the same will be true of minors and adolescents taken to the doctor by their families or by the police authorities. These cases are especially important from the social point of view; they are also the most dangerous ones, because of the addicts' age and their tendency to proselytize.

16. It is naturally a delicate matter to suggest some new departure or exception, but there are reasons to believe that a scheme along the lines of the French legislation on the struggle against venereal disease, embodied in title II of book II of the French Public Health Code, and on the organization of the treatment of dangerous alcoholics (title V of the same book) might well prove useful.

It is, however, necessary first to make disintoxication — i.e., the treatment of drug addiction — compulsory. If this were done, it could be made likewise compulsory to notify cases of drug addiction, with or without the name of the addict. Cases would be reported to the public health authorities by the doctor, omitting the name of the patient if he accepts treatment; a full report would, however, be filed if the patient refused treatment, or if the social conditions of the addict's life lead the doctor to the conclusion that he is a contagious addict.

These provisions could be supplemented, as in the case of the legislation against venereal diseases and dangerous alcoholics, by general provisions enabling the public health or judicial authorities to order the committal of an addict to hospital as a matter of course. It would be a question of reporting not drug addicts as such but those addicts who are dangerous to others, or who refuse treatment.

17. It is perhaps possible to obtain an idea of the results which could be expected from such an amendment of the relevant legislation by examining the manner in which cases of syphilis and tuberculosis, for example, are notified.

In France, these two diseases are classified as contagious diseases subject to compulsory notification. However, such notifications are very rarely made because, in spite of the explicit provisions of the law and the heavy penalties to which doctors are liable, they are reluctant to report cases of these two diseases, which, because of their chronic character and their profound social implications, make patients reluctant to disclose their exact nature.

The progress of medical science, however, has made it possible to cure certain types of tuberculosis, and this has brought about some change in the general outlook; doctors are now more concerned with the protection of young children against contamination by a patient who refuses to undergo treatment, for example.

A similar progress has become apparent in regard to syphilis, and the same would appear to be true of drug addiction when treatment is given in truly specialized centres. However, with regard to syphilis, because of its normally venereal origin, the number of notifications by doctors has not altered materially; physicians seem to prefer to treat their patients themselves and try to persuade them directly to take steps not to contaminate others. The position is different with regard to drug addiction: the doctor is generally not in a position to provide treatment himself, because that treatment requires admission to a hospital. Nor can the doctor himself ensure prophylaxis.

In cases of drug addiction, it would appear that the possibility of notifying the names of addicts, if necessary, can in certain cases serve to allay the conscience of a doctor who considers certain types of addict dangerous.

18. From this study, a number of facts emerge which appear to us fundamental in the progress of the struggle against drug addiction.

The total number of known or suspected drug addicts is still very large, but a new group of addicts has emerged which is very rapidly increasing, particularly in certain highly developed countries. This is the group of children, minors, adolescents and young adults. Their emergence as consumers of drugs is particularly alarming. They can form, in the rising generation, an active nucleus of drug addicts ready to replace those whom certain countries are endeavouring to suppress by legislative measures; they can become a source of moral and intellectual degradation.

In the struggle against drug addiction, certain measures should no doubt play a prominent part, such as those adopted by Thailand in regard to opium smoking; sources of drug supply must be stopped; the production, storing, trade and use of drugs must be brought under control; drastic measures must be taken, or those in force must be strengthened, against the illicit possession and sale of addiction-producing drugs, whether they are old drugs or new synthetic drugs; it is also necessary to organize everywhere, on a scale comparable with the relative importance of the evil in each country, specialized social and medico-social services capable of detecting and controlling cases of addiction, and providing addicts with treatment and after-care; it is necessary to compel addicts to undergo disintoxication and to punish recidivists, provided that the penalties are served in special penitentiary sections where treatment and after-care are provided.

To our mind, however, it is necessary to resort to every possible method of attack. The system of the registration of drug addicts makes it possible to get a picture of the progress of addiction in the various countries and to note with satisfaction the recession of the evil, or else detect any deficiencies in the system of the control in force. Registration also makes it possible to take appropriate individual measures.

The compulsory notification of cases of addiction by doctors, which proceeds from the same idea, can only make a small contribution to the solution of this grave problem. This fact, however, should be no reason to neglect it. Any attempt to make such a notification compulsory would, however, conflict in principle with the International Code of Ethics and with the rule of professional secrecy which we have examined in its various aspects; if, therefore, it is desired to introduce it, the manner must be examined very closely. To our mind, such a notification cannot be imposed indiscriminately in all cases.

A drug addict is undoubtedly an individual whose psychic faculties are affected. His willpower is lessened, as is his moral sense, which may even be completely paralysed. He cannot defend himself alone against his disease. Such a person is not always an ordinary patient. In certain cases, when a doctor detects addiction on examining the patient, or when a patient confides his condition to a doctor and asks for his professional assistance, there can be no question of the doctor reporting him to the authorities; this, however, is subject to the explicit condition that the doctor should not become an accomplice of the addict by prolonging his addiction, but should guide him rapidly and firmly to the weaning process and lead him to the specialized bodies which can provide him with the necessary moral after-care.

In other cases, it would appear that the drug addict should not be placed on the same footing as an ordinary patient, in regard to whom the doctor is under a duty to observe absolute secrecy. We believe that the answer to this difficult problem can be sought in measures similar to those adopted in the French legislation on the subject of drugs, contagious diseases and alcoholism.

As stated in section 14 above, although there is no obligation laid down in France to notify cases of a drug addiction by name, such a notification is in effect imposed in connexion with the prescription of narcotic drugs; the doctor is under obligation to make use of a special drug-prescription book in which the names and addresses of the patients must be entered. This is a form of indirect compulsory notification. The doctor does not commit a direct breach of medical secrecy; he records a treatment, and not a diagnosis. It is for the pharmacy inspection services to detect cases of drug addiction with the aid of the information thus given.

To our mind, however, these measures can be supplemented by the study of a new social legislation. Such legislation would impose the compulsory notification of cases of drug addiction, without disclosure of the names of addicts, if the latter consent to be treated and do not seem to present any danger to themselves and others. On the other hand, in the case of dangerous individuals capable of active proselytism, of addicts who refuse treatment, and of minors, the notification would specify the name. The same would be true, of course, in all cases coming to the knowledge of doctors in observation and treatment centres for delinquent minors.

19. The reply to the question embodied in the title of this article must therefore be an extremely complex one: it is not consistent with the ethics of the medical profession to notify cases of addicts who come to a doctor for treatment or of addicts detected in the course of somatic examination following a consultation with a view to treatment, provided that the addict concerned accepts disintoxication treatment; on the other hand, a doctor may report to the authorities those who, without any medical reason, seek to obtain from him a prescription which will enable them to continue to take drugs more or less legally or who, because of their age or their propensities to active proselytism, constitute a serious moral danger.

Hong Kong's prison for drug addicts

NOTE: *A steep-sided valley in the British Crown Colony of Hong Kong is being transformed into a model prison — by drug addicts. The results being achieved by the addicts are spectacular, but the real value of the scheme lies much deeper. The following article written for the* Bulletin *by the authorities in Hong Kong gives an account of the Tai Lam prison for addicts.*

A White Paper published in Hong Kong in November 1959 conservatively estimated the number of drug addicts at 150,000 to 180,000; it also stated that some experts closely connected with anti-narcotic work, either in an official or unofficial capacity, placed the total as high as 200,000 to 250,000. This means that, on a population estimate of slightly more than three million, the incidence of drug addiction is among the world's highest. On current prices, and taking the lowest estimate of the number of addicts, at least 170 million Hong Kong dollars a year (£10,625,000 sterling, or $29,824,560) is being spent on diacetylmorphine (heroin) and opium.

The magnitude of the problem is largely due to the fact that Hong Kong is a free port, possessing entrepot facilities designed to encourage the freest possible flow of regional trade. This freedom of movement, vital to Hong Kong's economic well-being, is being exploited by international traffickers in narcotic drugs. The problem is complicated by the fact that, in recent years, attempts by the Hong Kong Government to suppress opium smoking have resulted in traffickers and addicts turning increasingly to heroin, a drug much easier to smuggle and conceal.

As in other parts of the world, addiction is most pronounced among the criminal element of the population, and between 1955 and 1958 the percentage of narcotics addicts among persons sent to prison rose from 46 to just over 60. There was an obvious need for a special prison for the rehabilitation of

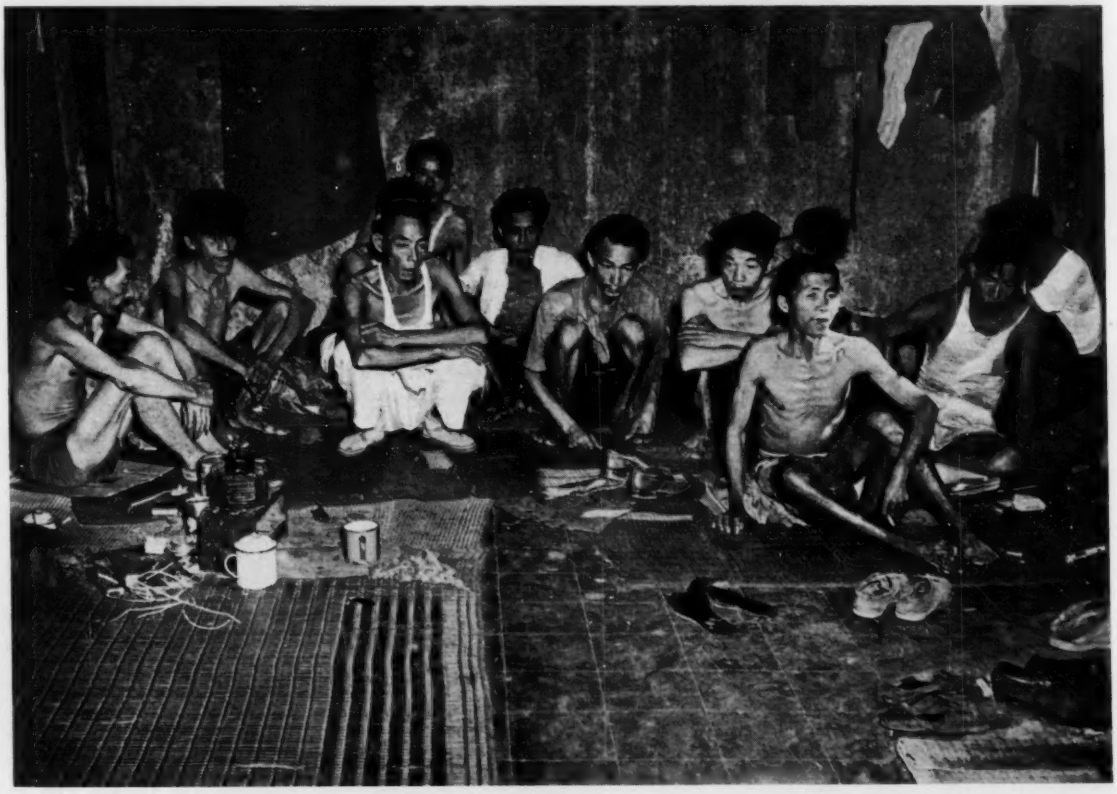

FIGURE 1

Drug addicts in a typical " divan ". Such places are situated in tenements, and the operators rarely remain in one place more than a few days for fear of detection.

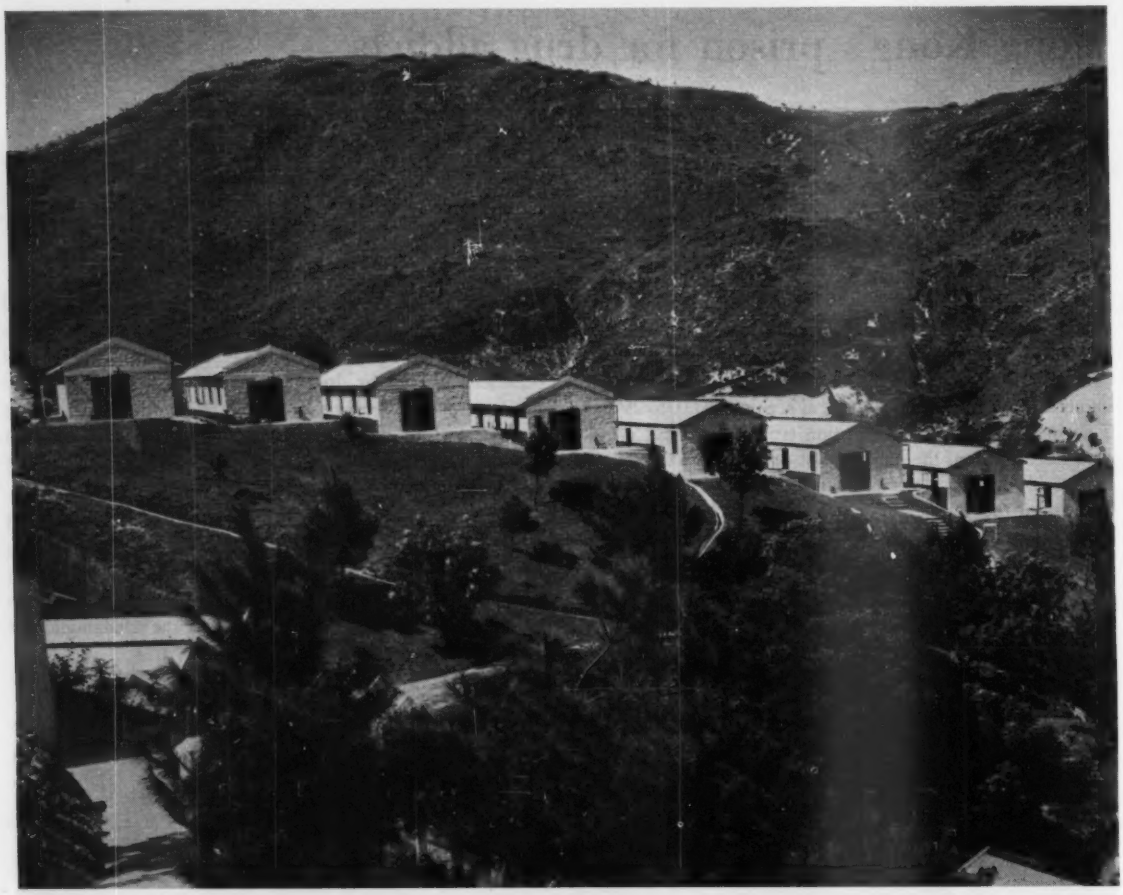

FIGURE 2

Prisoners' barrack-blocks surrounded by lawns and trees. Forty or sixty prisoners sleep to a block, and all windows are left open at night.

addicts, and the site chosen was at Tai Lam, 16 miles from Kowloon, where work had recently ended on a large dam. Close to the dam were well-built stone huts with asbestos roofs, which had been used to house workers; on an attractive headland a mile away were 14 bungalows built for the resident engineers. It was an excellent location for a specialized prison, and the first batch of addicts was moved there in November 1958.

The prison accommodation is on a hillside, and consists of 15 single-story buildings, two of which are used as a hospital and tuberculosis ward, with a smaller building for the medical officer and staff. All buildings have their own flush system, and there is a communal bathroom with 60 showers. Reception office, kitchen, stores and workshops are situated some distance away on the floor of a valley below the dam.

The prison is divided into three progressive sections — the hospital, a light-labour section, and a full-labour section. The hospital is for prisoners with physical ailments and those suffering so severely from malnutrition that they cannot work. The light-labour section provides useful but not too heavy work, such as gardening, for prisoners slowly regaining their lost health and strength.

Tai Lam prison can accommodate 680 prisoners, and is always full. More than 70% of the prisoners were convicted for possession of heroin. Most of the remainder had barbiturates, while a very few were found in possession of opium. (In Hong Kong, many addicts employ barbiturates as a base powder during the smoking of heroin because of their volatility. In August 1958 legislation was therefore enacted to place barbitone, phenobarbitone, and their salts and preparations under very stringent controls, the unauthorized possession of which is now a serious offence.) Admission to Tai Lam is not, however, restricted to men convicted of drug offences.

Records also show a close connexion between drug addiction and other forms of crime. In 1959, over 60% of all prisoners convicted in Hong Kong were on drug charges. Not all were addicts, however; many of them, particularly women, were drug carriers. Conversely, many prisoners convicted

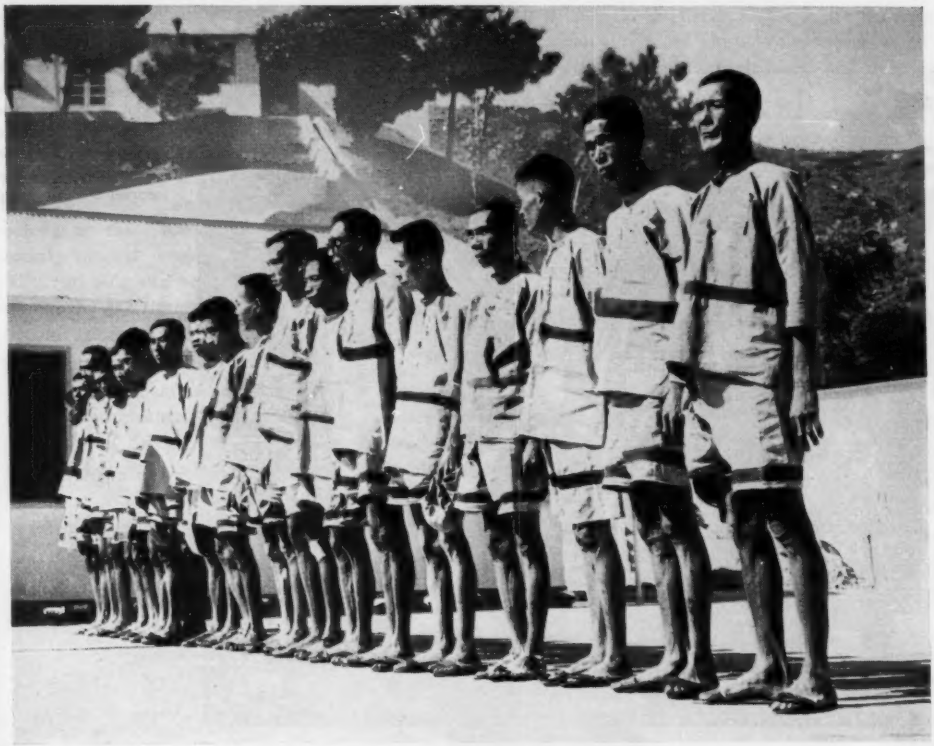

FIGURE 3

A new intake of prisoners lining up for inspection.

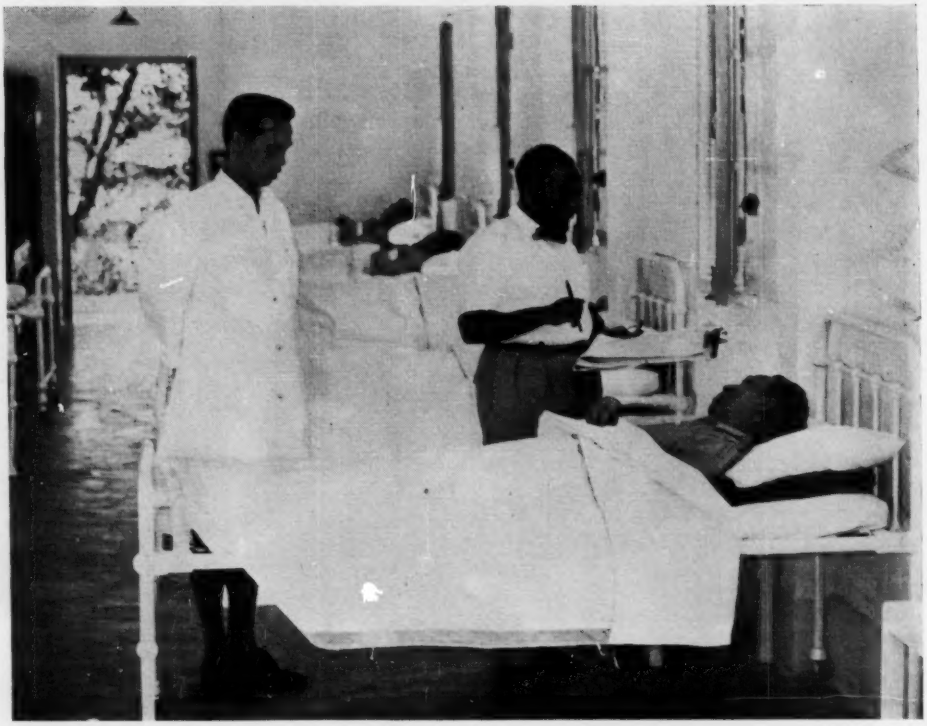

FIGURE 4

Indian medical officer attending seriously ill addicts in prison hospital. Most have tuberculosis. Less serious cases are given special diet and put on light duties.

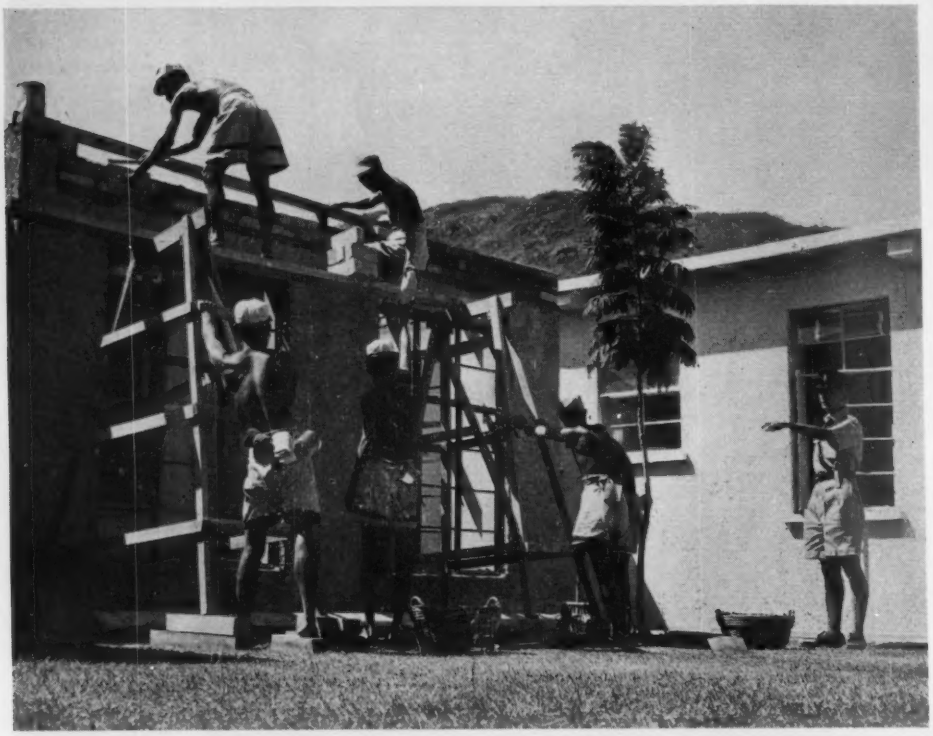

FIGURE 5

Addict prisoners working on building. In addition to converting barrack-blocks to kitchens and offices, they built a swimming-pool and helped the Forestry Department to plant young trees.

FIGURE 6

Cookhouse duty is popular, because cooks are paid 1.20 dollars a week, compared with 80 cents for other workers and 40 cents for hospital patients.

on charges having nothing to do with drugs are addicts. Many were once in decent employment, but have sunk lower and lower as more and more of their earnings went on drugs, finally taking to crime to obtain money to satisfy their craving.

Most addicts are between 20 and 40 years of age. Very small numbers of teenagers have been convicted (in nearly all cases they were shown to have picked up the drug habit from parents or friends). Over half of the convicted addicts belong to the " lower classes " — that is to say, they are mainly manual workers paid by the day — while between 30% and 40% can be described as " white collar " workers, though by the time they are convicted they may well have become unemployed, with consequent lowering of social status.

The predominant cause of addiction is association. Addicts try to induce others to use drugs because they believe that supplies will become easier if a large " market " is assured; pedlars of course are always on the lookout for new customers. Another important factor is the widespread belief that drugs can cure tuberculosis, coughs, pains of all kinds, piles, hernias, rheumatism, stomach ulcers and dysentery.

Before being sent to Tai Lam all addicts spend from seven to ten days in Victoria prison, Hong Kong, for the " withdrawal period ". Deprivation symptoms are not serious unless complicated by disease dangerous to life, and replacement drugs are not normally given. By the time they reach Tai Lam the addicts are becoming accustomed to facing life without drugs, but by no means all are fit for immediate employment. Constant use of drugs has sapped their resistance, leaving them easy prey to disease and malnutrition.

About 20% have tuberculosis, and the worst of these go straight to hospital for complete rest. The remaining TB cases are given daily treatment and special diet including milk, eggs and vitamins, and put on light duties, which means they are allowed to do very light work in the gardens.

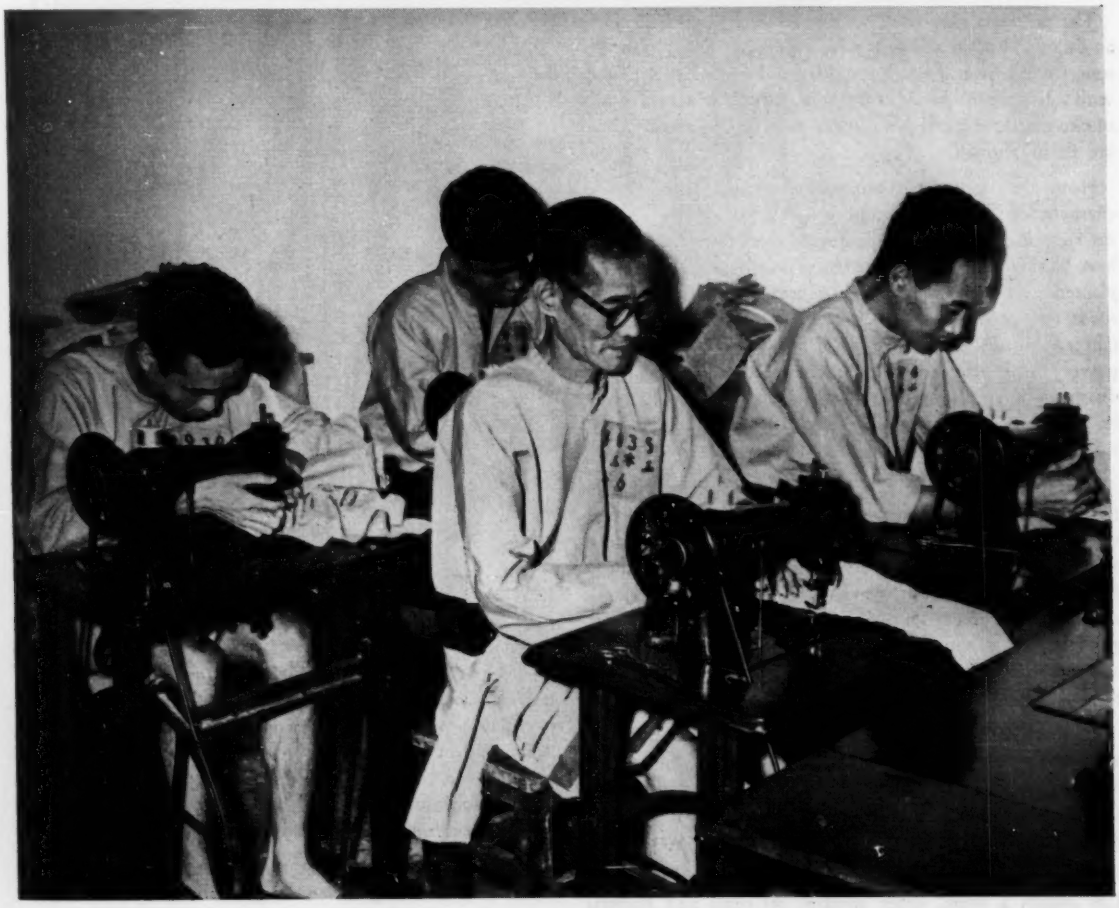

FIGURE 7

Tailors making uniforms for prisoners. They must of necessity work indoors, but the majority of prisoners are kept in the open air, working on building projects and gardens.

In the physical rehabilitation programme the following considerations are given priority:

To free the prisoner from addiction in any particular field of indulgence;

To treat any disease complicated by addiction;

To rebuild physical strength and bring it up to normal standard.

Tai Lam is a minimum-security prison, which means it is a new experience even for those many addicts who have previously served sentences elsewhere. Forty or sixty prisoners live in barrack blocks, where the windows are left open at night.

There is no slackening of essential discipline, however, and the rules are insisted upon. As in other prisons, prisoners are allowed to talk, provided they do it quietly. So far no prisoner has tried to take advantage of the regime. Apart from knowing they are comparatively well off, prisoners regard their stay at Tai Lam as something more than just another prison sentence.

The prisoners' day starts with reveille at 6 a.m. Meals are at 7 a.m., 12 noon and 4.30 p.m. Lights out is at 9 p.m. Prisoners work from 8 a.m. to midday and from 1 to 4.15 p.m. with a ten-minute break every hour, during which they may smoke the three cigarettes allowed each day to all those who are fit or semi-fit.

From the start the rehabilitation programme has been energetic and positive, because it is felt that the provision of the right kind of work is the key to rehabilitation. Prisoners have been employed on afforestation on a large scale, and have planted over 200,000 trees. They have constructed forestry roads and paths, and have carried out various projects at Chinese villages which had neither the resources nor manpower to do the work themselves. Recently, following disastrous floods, they rebuilt dykes and constructed new bunds in ricefields. They frequently have to walk three or four miles to reach the work site.

At Tai Lam itself the prisoners have completely changed the appearance of their prison. When the first batch of convicted addicts moved in, the ground was ankle-deep in mud and the hillside bore the scars of erosion. Now the site is properly drained by concrete channels built by the prisoners, and lawns and young pines planted during the past two years give the prison a park-like appearance. The prisoners' latest accomplishments are the building of a 60 ft. by 30 ft. swimming pool and the turfing of a sports field.

Every effort is made at all times to employ as many prisoners as possible outdoors, and on a typical day recently only thirty-three essential workers such as cooks, tailors and carpenters were indoors. To get maximum benefit from the sun and fresh air, prisoners work stripped to the waist.

As in all prisons, payment is nominal. Cooks receive 1.20 dollars a week, other workers 80 cents and hospital patients 40 cents (the Hong Kong dollar is worth 1*s.* 3*d.* sterling, and about 18 U.S. cents). Biscuits, chocolate and toilet articles are on sale at the prison shop.

The underlying theme at Tai Lam is a humanitarian approach to drug addiction. How far is it succeeding? It is too soon to compile reliable figures of recidivism, but of the 1,388 prisoners discharged during the first year of Tai Lam's existence, only 65 were again convicted. It has already been amply shown that addicts respond to conditions at Tai Lam by taking a new interest in life much more quickly than could be expected in a conventional prison. Bodily, most gain from 12 to 16 lb.

Changes in weight of typical prisoners at Tai lam prison, Hong Kong

Prison number	Sentence (months)	Date of discharge (1960)	Weight		Gain or loss (lb)
			On admission (lb)	On discharge (lb)	
2629	9	1 Jan.	101	125 ½	24 ½
2839	7	1 Jan.	83 ½	121 ½	38
2245	12	2 Jan.	124	139 ½	15 ½
2641	9	2 Jan.	109 ½	121 ½	12
2251	12	2 Jan.	117	131	14
2252	12	2 Jan.	102	114	12
2646	9	2 Jan.	119	124	5
2269	12	4 Jan.	104	118 ½	14 ½
3059	4	4 Jan.	96 ½	116	19 ½
2286	12	5 Jan.	111	123 ½	12 ½
2649	9	5 Jan.	116 ½	132	15 ½
2785	8	5 Jan.	109	124	15
2300	12	6 Jan.	94	114	20
2311	12	6 Jan.	119	141 ½	22 ½
2328	12	6 Jan.	132	134	2
2347	12	6 Jan.	105	124 ½	19 ½
2652	9	6 Jan.	97	111 ½	14 ½
2789	9	6 Jan.	111 ½	127 ½	16 ½
2791	8	6 Jan.	118 ½	125	6 ½
2658	9	7 Jan.	100 ½	124 ½	24 ½
2661	9	7 Jan.	110 ¾	126	15 ¼
2669	9	8 Jan.	107 ½	123	15 ½
2795	8	8 Jan.	100	120	20
2797	8	8 Jan.	116 ¼	137	20 ¾
2869	7	8 Jan.	120	137 ½	17 ½
2873	7	8 Jan.	103	127	24
3099	4	8 Jan.	118 ½	116 ½	—2
3100	4	8 Jan.	112 ¾	120	7 ¼
3101	4	8 Jan.	136 ¾	141 ½	4 ¾
2322	12	9 Jan.	103	123 ½	20 ½
2678	9	9 Jan.	106 ½	127 ½	21

The superintendent of Tai Lam prison wrote at the end of its first year: " Results have proved that hard, outdoor work can play a major part in getting prisoners into good shape again, and in helping them to forget their addiction. It has been proved beyond doubt that prisoners who work in the hills, walking long distances each day, improve and put on weight more rapidly than those on light labour.

" I am convinced that the three essentials for the speedy rehabilitation of drug addicts are good food, vigorous exercise in the form of work, and fresh air."

The Commissioner of Prisons stated recently: " We know that a large number of prisoners go out cured and determined

FIGURE 8

Prisoner due for release. During the time he was at Tai Lam he gained more than 14 lb in weight. He told the photographer, " I'll never come back to prison again. No more drugs for me."

not to return to the drug habit. There are four full-time after-care officers following up cases selected from those most needing help, and it is upon the results of their work that we shall be able to assess the value of Tai Lam.

" Meanwhile, we can say that the prison has brought hope where there was none before, and a real chance of a new life for those who previously lacked proper treatment. The drug habit is deep-rooted and will take years of education and a rising standard of living to eliminate. Tai Lam will play its full part."

Manufacture of alkaloids from the poppy plant in Hungary

By Dr. Istvan Bayer
Secretary, Hungarian Pharmacopoeia Commission

Since Sertürner's discovery, many research workers have attempted to produce morphine from poppy capsules — i.e., without going through the opium stage. A large number of failures were registered before Tilloy (1) in France and F. L. Winckler (2) in Germany succeeded in preparing morphine from poppy capsules. Their methods are of purely historical interest; those methods could not compete with the production of morphine from opium, so that opium remained the raw material in morphine manufacture. In the majority of European countries, attempts were made to produce opium itself from poppy capsules — in Hungary, for example, E. Deér (3) produced 4 cg of opium with a morphine content of 15-16% per capsule at Aszod — but these experiments are only of scientific interest; there was no actual production of opium, as this would have been uneconomical in view of European salary rates.

FIGURE 1
Statue of János Kabay at Tiszavasvári

The manufacture of morphine direct from poppy straw was only achieved one century after the first experiments. In 1925, a young Hungarian, J. Kabay, devised a method (4) for the production of morphine from green poppy plants; in 1927, he founded in his native country a small chemical factory under the name of "Alkaloïda". On 14 March 1930 (5), Kabay reported as follows to the Hungarian Pharmaceutical Society:

"The poppies are cut shortly after flowering. The usual method of harvesting is for the plants to be mown down and sheaved. The extracting machine is carried wherever the harvesters go, so as not to have to move the whole crop. The plants are weighed, then finely chopped and crushed. After a preliminary pressing these are fed into the extracting machine, where they are continually mixed with the extracting liquids.

"The extract and the juice emerging from the press are carried in barrels to the factory, where the liquid is concentrated into a soft extract and is stored in barrels. This pasty substance has a morphine content of 0.4% to 0.8%; there is no risk of deterioration, because it contains preservatives in sufficient quantity, and it can therefore be stored without loss.

"This phase of the manufacturing process is seasonal; the season varies in duration, and occurs between 15 May and 15 July.

"The second phase of the manufacturing process is the conversion of this concentrated extract into raw chlorophyll and a complex mixture of alkaloids."

This process is very costly and also technically complicated. The most serious difficulties involved are due to the presence of poppy-seed oil and chlorophyll. Other difficulties are described by Kabay (6) (7) in his patent specification of 30 November 1931, in which he made known the principle of the extraction of morphine from poppy straw:

"Although the yield with this process is high and the opium alkaloids obtained are pure, the process has the disadvantage that it can be employed only at the season when the poppy plant is between the stages of blooming and maturity. This period is very short, so that it is difficult to manufacture with profit. Moreover, the cost of transporting the green plants is high, owing to the space required and to their weight, and the seed product is lost.

"The invention depends upon the surprising discovery that the opium alkaloids can be obtained from the poppy plant

even when the plant is already ripe and dry. According to the invention, the ripe and dried plant portions are, for this purpose, suitably cut up, then treated with an extracting fluid, and the extract obtained by means of the extracting fluid is treated for opium alkaloids."

The Kabay family commenced production of alkaloids on a very small scale, but the importance of the above process became apparent within a few years (see table 1).

TABLE 1 (3)

Year	Morphine imports into Hungary (kg)	Morphine exports from Hungary (kg)
1927	991	—
1928	145	—
1930	49.7	12.6
1933	19.2	63.2
1934	2.6	79.6

In the beginning, J. Kabay not only had to struggle against technical and financial difficulties, but also the accusation that the manufacture of morphine in Hungary would facilitate the spread of addiction. The technical difficulties were surmounted; the financial problems were solved with state assistance, and the accusation regarding the spread of addiction was refuted in Hungary and abroad by publishing the manufacturing process. In 1934, a League of Nations committee visited Hungary (8); this visit represented a great honour, and a well-deserved one for Kabay. As a result, expert opinion realized not only that the Kabay process for the production of morphine is of great economic importance (because it makes use of waste material), but that it plays an even more significant role in public health; the omission of the "opium" stage has made it possible to produce, under complete control, morphine and other alkaloids from the poppy plant by using a raw material which is not itself a narcotic.

Worn out by over-work and disappointment at public misunderstanding, Kabay died at the early age of forty. Before he died, he was able to devise a chemical method of determining the morphine content of poppy straw, a task which was entrusted to him by the League of Nations (9) (10), but he was unable to give a lecture at Geneva on his work.

The great importance of the process was also recognized abroad. In Switzerland, Hoffmann-La Roche was the first to produce morphine from poppy capsules (11); Poland and Czechoslovakia began producing morphine, making use of the Kabay patent.

Figure 2 shows the development of crude morphine in Hungary, and illustrates the very rapid growth of that production.

In 1958, the Hungarian People's Republic was the sixth producer of crude morphine in the world, being outstripped only by a few more densely inhabited and more highly industrialized countries (see table 2).

In the manufacture of morphine from poppy straw, the Hungarian People's Republic held the first place in 1958 with 34%; it produced 50% more than the quantity produced by the Netherlands, which held second place (see table 3).

One can have the assurance that the whole production of alkaloids manufactured from poppy plants in the Hungarian People's Republic serves to meet, in part, world morphine

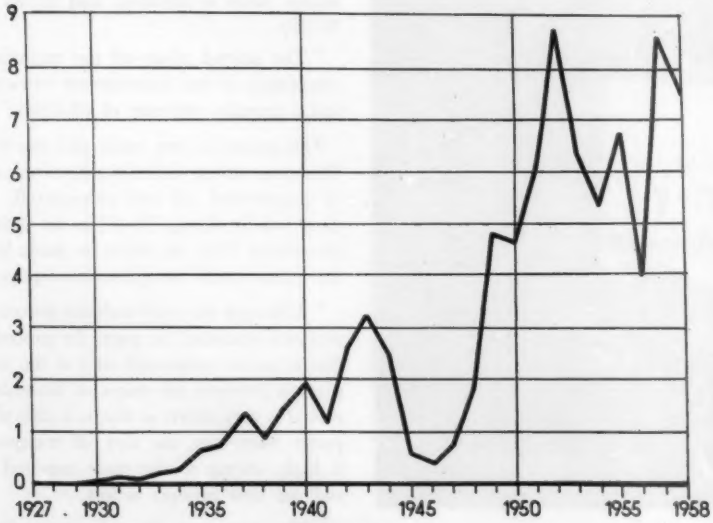

FIGURE 2 (12)

Production of crude morphine in Hungary, 1927-1958 (vertically tons, horizontally years).

TABLE 2

World manufacture of crude morphine in 1958 (13)

Country	Morphine manufacture	
	Quantity (kg)	Percentage of world total
Total world manufacture	111,854	100
including:		
United States of America	17,477	15.6
United Kingdom	17,393	15.6
Union of Soviet Socialist Republics..	15,826	14.2
Federal Republic of Germany	13,271	11.9
France	9,300	8.3
Hungarian People's Republic	7,479	6.7
Netherlands	5,594	5.0
Japan	3,566	3.2
Belgium	3,376	3 0
Polish People's Republic	2,743	2.5
Italy	2,354	2.1
Czechoslovak Republic	1,470	1.3
Argentina	1,437	1.3

needs, because the perfect control system ensures that none of the production is diverted into the illicit traffic.

The quantity of morphine produced depends on a number of factors, the chief one being raw-material supplies; the second is the process of manufacture.

The poppy plant (*Papaver somniferum* L.) has been grown for centuries in Hungary and in other central European countries, where the poppy seed is an article of general consumption.

In Hungary, the species of poppy plant more generally grown has a dark-coloured seed, whereas the capsule from the Far Eastern plant contains a light-coloured seed.

The oil content of the seed is 40 to 50%. Poppy-seed oil (known in the trade in French as huile d'œillette) is used for human consumption, but is also much sought as a solvent for pigments in painting because of its quick-drying properties. The extensive use made in Hungary of the poppy seed has rendered necessary the cultivation of the poppy plant on a large scale.

Until about 1930, poppy straw, a waste product of the cultivation of the poppy plant, was used as an inferior-quality fuel; wherever possible, some use was made of it for cattle bedding.

J. Kabay was the first to draw attention to the possibility of using poppy straw as a raw material for the extraction of alkaloids; until then, as we have seen, this straw was used for purposes of minor importance.

The poppy-seed needs of the Hungarian People's Republic amount to some 5,000 tons annually. About 70% to 80% of this quantity is grown on large holdings, the remainder being grown in vegetable plots, or as a catch crop in intercrop.

For the last thirty years, the area under poppy cultivation has varied in direct relation with price fluctuations of the poppy seed in the world market. The area under cultivation and the volume of poppy straw reached a maximum during the years 1950-1954; they decerased steadily during the subsequent years. During the latter period, there have been years during which the quantity of poppy straw produced, including that from catch crops and vegetable plots, did not even yield the quantity of raw material needed by the alkaloid industry.

At present, the area under poppy cultivation in individual holdings is greater than that in state undertakings and agricultural co-operatives, but that in state undertakings is growing from year to year, which is a good sign.

TABLE 3

World manufacture in 1958 of crude morphine from poppy straw (13)

Country	Manufacture of raw morphine from poppy straw		
	Quantity (kg)	Percentage of world total	Percentage of national manufacture
Total world manufacture*	22,003	100	
including:			
Hungarian People's Republic	7,479	34.0	100
Netherlands	5,590	25.4	99.9
Polish People's Republic	2,749	12.35	100
Czechoslovak Republic	1,470	6.7	100
Union of Soviet Socialist Republics	1,016	4 6	6.4
Federal Republic of Germany ...	25	0.001	0.2

* This quantity represents 19.7% of the total world manufacture of crude morphine (mainly from opium and poppy straw).

TABLE 4

Area under poppy cultivation (12)

Period	Area under poppy cultivation (holds) *
1930–1934	20,760
1935–1939	13,815
1940–1944	15,255
1950–1949	13,538
1945–1954	19,355
1955–1958	15,101

* The "hold" is a Hungarian unit of surface measurement equivalent to 0.57 hectares.

TABLE 5

Area under poppy cultivation in state agricultural undertakings

Year	Holds
1955	285
1956	988
1957	1,376
1958	2,470
1959	2,621

In view of the increase in the designed capacity for production of the Alkaloïda factory, the increase in the area under cultivation seems justified, particularly since it is desirable to stock poppy straw in years when there is a good harvest, to meet the deficit from bad harvest years. This would ensure the smooth production and export of alkaloids.

Our country has so far exported alkaloids produced from the poppy plant to some thirty different States. In order to meet our export commitments, we have been obliged, from time to time, to import raw material to remedy shortages of poppy straw. We imported poppy straw from Romania in 1952-1954, from Bulgaria in 1954, from Yugoslavia in 1956 and from the USSR in 1959; we have even been obliged, on occasion, to make certain imports of opium from Turkey, thus raising unduly production costs.

If we maintain an adequate area under poppy cultivation, and select for the purpose suitable varieties of the poppy plant, poppy straw supplies to suit the capacity of the Alkaloïda chemical factory would seem to be assured.

Since 1951, several experiments have been made for the purpose of selecting an improved variety of poppy plant with a morphine content higher than the 1951 average; among others, the results obtained by Professor S. Särkaùy (14, 15) may be mentioned.

In the production of alkaloids from the poppy plant, the question of the process of extraction is second in importance only to that of the poppy-straw supply.

Kabay's original process (3-7) has been improved in the last twenty-five years, but the method used in the production of alkaloids from poppy straw remains basically the same.

The Kabay process is as follows: The poppy capsules (with stalks not more than 10 cm in length) are thrashed, dried and then treated with an extracting liquid which consists of a solution of sodium bisulphite in water. The resultant aqueous extract is concentrated in vacuo using the " counter-current principle " method until it attains a syrupy consistency. The pasty substance thus obtained, which has a morphine content of 1% to 1.2%, is then treated with alcohol or other organic solvent. The solution — which, besides morphine, contains a lesser amount of other extractable material than the aqueous extract — is then distilled, yielding an extract having a morphine content of 2% to 4%. From this mixture of alkaloids in alkaline medium the morphine base can be precipitated by treating the mixture with ammonium sulphate in the presence of benzene. The product will have a morphine content of over 50%, and, by means of repeated precipitation or crystallization, it is possible to obtain from it the pure morphine base and morphine salts or semi-synthetic derivatives.

The process has the serious disadvantage of a very low yield, a disadvantage of Kabay's original method, which has not yet been eliminated; with this process, only part of the morphine in the plant is extracted.

Between 1951 and 1958, the yield at the Alkaloïda factory at Tiszavasvári was at the rate of 49% to 54%. There are three possible ways of increasing the yield, and it is proposed to try all three in the factory. One method of raising the coefficient of extraction is to work at higher temperatures, while continuing to use sodium bisulphite solution as the extracting fluid. The second method of increasing the quantity of morphine extracted is the process involving the use of chalk. In certain countries, these two methods are combined. The third method is to use organic solvents instead of water for the extracting fluid. The most frequently used organic solvent is 2-butanol.

Improvements in the Kabay process are being directed towards simplification and the attainment of the highest possible degree of perfection in the preparation of alkaloids other than morphine, and in the conversion of natural alkaloids into semi-synthetic derivatives.

The Alkaloïda factory also produces large quantities of the following natural alkaloids: codeine, noscapine (narcotine), narceine and thebaine.

The following methods have been devised and developed in the Hungarian People's Republic by Prof. R. Bognár, who has published the following processes (16):

Raw morphine is precipitated in the presence of benzene.

Morphine is not very soluble in benzene, which readily dissolves the secondary alkaloids. From this solution in benzene, it is possible to extract codeine, noscapine (narcotine), and thebaine. These three alkaloids can be obtained or separated in two ways.

(*a*) The alkaloids may be extracted by treating the benzene solution with 0.02N sulphuric acid, the amount used being calculated by titration. If the sulphuric acid solution thus obtained is left in a cool place, the codeine sulphate will crystallize (this process for obtaining natural codeine has been known for a long time in the factory). The remaining benzene solution is treated with an excess of acid, and the acid solution is then combined with the acid mother-liquor of the codeine sulphate; an alkali treatment of the resulting solution will liberate all the alkaloids in an amorphous raw mixture. The mixture is treated with alcohol, and the noscapine base, which is not very soluble in alcohol, will crystallize. Tartaric acid, the amount used being determined by titration, is then added to the mother liquor. The solution is allowed to stand for one or two days, which results in the separation of crystals of thebaine bitartrate; these can be purified by re-crystallization in water, yielding a product from which the pure base can be obtained.

(*b*) Another method which is used to extract all the alkaloids present in the benzene solution is that of treatment with acid; the acid solution is then washed with caustic soda, thus freeing the alkaloids. From the amorphous mixture of alkaloids thus obtained, the noscapine is then extracted by crystallization from alcohol; the thebaine is then extracted in the form of the bitartrate and, after extraction from the mother liquor, the codeine sulphate, which is not very soluble, is precipitated from the aqueous solution.

The bulk of the natural narceine remains in the aqueous solution of morphine compounds thus obtained. The solution

FIGURE 3
The Alkaloïda factory in Tiszavasvári

is allowed to rest for a comparatively long time — one or two months — with, as a result, the separation, together with various other substances, of narceine, which can be purified by repeated crystallization. Of course, narceine can be prepared by the well-known method of using noscapine chlormethylate.

It is not economical to extract natural papaverine, as this alkaloid is present only in small quantities and its price is comparatively low; the fact should, however, be mentioned that 50% of the total world needs of papaverine are synthesized in the Hungarian People's Republic (Chinoin chemical and pharmaceutical laboratory, Ujpest). Our country is the world's greatest exporter of papaverine.

The Alkaloïda factory is manufacturing increasingly large quantities of hydrogenated derivatives of morphine and codeine (16), but codeine and ethylmorphine remain to this day the most important semisynthetic alkaloids. Table 6 shows the development of the production of these alkaloids.

TABLE 6

Production of codeine and ethylmorphine in Hungary (12)

Year	Codeine pure base	Codeine hydrochloride	Codeine phosphate	Ethylmorphine hydrochloride
	Quantity in kg			
1943...	163	879	718	371
1949...	836	898	1,775	1,076
1950...	1,039	775	2,678	356
1951...	967	1,471	3,044	424
1952...	1,759	1,705	3,564	921
1953...	1,284	905	3,591	482
1954...	1,259	1,120	2,121	538
1955...	1,431	1,422	2,296	762
1956...	955	776	1,494	527
1957...	1,347	1,445	4,954	924
1958...	1,193	1,680	4,117	1,017

World production of morphine varies in direct ratio with codeine consumption. Eighty-seven per cent of raw morphine is converted into codeine, and 7% or 8% into ethylmorphine, so that only approximately 5% or 6% is used in the form of morphine. The estimated total world consumption of morphine has steadily decreased; it stood at about 9 tons in 1934, but fell to approximately 5 tons for 1959. On the other hand, the estimated requirements of morphine for conversion have constantly increased; for 1934, the figure was approximately 33 tons, rising to approximately 106 tons for 1959. The increased consumption of codeine and ethylmorphine clearly stems from the increase in world population and the rise in levels of living, combined with the extension of medical and welfare services in many countries where these services did not exist in 1934. However, the quantity of opium available was not sufficient to produce the estimated 111 tons of raw morphine required for 1959 (17). Thus, in 1955, instead of the estimated 105 tons, only about 88 tons of morphine were produced.

It must be remembered that world opium production, which was of the order of 1,295 tons in 1953, fell to 939 tons in 1958, a decrease of 32% (13). Accordingly, there could be no question of decreasing the quantity of 22 tons of morphine produced from poppy straw in 1958 throughout the world (corresponding to the morphine which would be produced by approximately 140 to 160 tons of opium), but on the contrary, to increase it by every legitimate means.

Now it is obvious that the restrictions contemplated in the third draft of the Single Convention on Narcotic Drugs (18) would certainly lead to a decrease in this type of production.

Moreover, the decrease in world opium production has led to a reduced level of reserve stocks. Total reserve stocks throughout the world were of the order of 1,744 tons at the end of 1953, but, at the end of 1958, these stocks had dwindled to approximately 840 tons, representing a little less than the total licit world consumption for one year.

For this reason, the Hungarian People's Republic considers that it should make every effort to increase the production and export of alkaloids prepared from poppy straw.

Hungarian exports of alkaloids from the poppy plant started to develop in 1942; in recent years they have varied between 6 and 8 tons annually. In 1958, the Hungarian People's Republic exported 24.6% of the morphine exported throughout the world, being in this respect second only to the Netherlands, which exported 50.8% of the world total. With regard to codeine, our country held third place, with 15.5% of the total exports, the United Kingdom being first with 34%. As to ethylmorphine, our country held second place with 29%, being led by the United Kingdom (13).

Any provisions which might interfere with the freedom to grow the poppy plant for the purpose of producing the edible poppy seed would have the counter-effect of spreading drug addiction. Such provisions would reduce the quantity of alkaloids extracted from the poppy straw; in order to replace the missing quantity, other countries would soon increase their production of opium, which is more difficult to control than poppy straw.

This fact was stressed by the Hungarian delegation at the thirteenth and fourteenth sessions of the United Nations Commission on Narcotic Drugs, when the Commission discussed the third draft of the Single Convention on Narcotic Drugs (18). Noting the objection by several States to the provisions of the draft Single Convention relating to poppy straw and cannabis, the Commission agreed to insert the following general observation as a footnote, after article 30 of the draft Single Convention:

"The countries mentioned below wish to have recorded objections or reservations with respect to all the provisions of the Convention, in so far as they related to poppy straw and to the production of cannabis: Austria, Canada, Czechoslovakia, Federal Republic of Germany, France, Hungary, Italy, Switzerland, the United Kingdom and Yugoslavia."

Throughout the world, great hopes are being placed on the entry into force of the draft convention, which would constitute a great step forward in the struggle against the abuse of narcotic drugs. In this spirit, all governments support the aspirations of those countries which wish to produce alkaloids from the poppy straw, a raw material which, unlike others, cannot be used as a narcotic drug. However, a rigid application of the convention, which would leave no scope for reservations, would prevent the extraction of alkaloids from poppy straw in the event of a shortage of opium. That shortage would, in its turn, lead to that of alkaloids, and result in a great increase in the price of alkaloids in the world market. Therefore, encouragement of the production of morphine from poppy capsules is fully consistent with the spirit of a single convention. A more strict control is possible of that production than of the extraction of morphine from opium.

The control of this process is quite different from that of the manufacture of morphine from opium. This fact was noted as early as 1934 in document O.C.1546 (1) reproduced as annex 3 to document O.C.1562 (1) of the League of Nations (memorandum submitted by the Secretariat following the visit to Hungary of a member of the Opium Section), which contains the following passage (8):

"From the administrative point of view, the control of poppy straw as such must be regarded as superfluous; it is not dangerous in itself and is unlikely to pass into the illicit traffic. Moreover, its control as raw material actually utilized for manufacture is greatly facilitated for the reasons mentioned above— namely, the impossibility of concealing the raw material, or of clandestine manufacture (see paragraph 11)."

Paragraph 11 of the memorandum states:

"As large quantities of poppy straw are required for manufacture, it is impossible, in practice, to conceal the raw material. As, moreover, manufacture cannot take place in small laboratories, but only in large factory premises, secret manufacture is practically impossible."

It would be in keeping with the whole tenor of the convention to encourage this type of production, which makes possible a much more effective control than the manufacture of morphine from opium. When the poppy seed has been removed by thrashing, the poppy capsules, with their stalks, constitute agricultural waste products; these products become a raw material for the production of alkaloids only if they are gathered and delivered to state purchasing agencies. It is only at the subsequent stage, within the framework of the manufacture of morphine, that rigorous control must be exercised.

Moreover, the designation of the areas in which cultivation of the opium poppy, for the purpose of producing poppy straw, should be permitted, presents insurmountable difficulties. In Hungary, the poppy seed is part of the people's diet, and hundreds of thousands of cultivators grow the poppy plant not only on large plots, but also as a catch crop and even in vegetable plots, making it impossible to introduce a control system like that contemplated in the convention. In practice, it is impossible to require the delivery of the total crop of poppy straw, because cultivators burn part of it and use part as bedding for cattle. Besides, the stalk, apart from the capsule and the 10 cm immediately below it, is not suitable for manufacturing purposes.

As we shall explain, however, an automatic control exists in connexion with the delivery of the poppy.

Well before the commencement of the agricultural year, the purchasing agencies enter into contracts with the state agricultural undertakings, the co-operatives and the cultivators of individual plots, to guarantee the production and delivery of

a certain quantity of poppy seed; the delivery of the quantity of poppy seed purchased entails that of a corresponding quantity of straw.

Large purchases are made by the Alkaloïda chemical products factory itself, or by the Federation of Medicinal Plant and Silk Cocoon Co-operatives. The Federation of Market Agricultural Products Co-operatives also purchases smaller quantities.

The weight of the poppy straw is approximately equal to that of the poppy seed harvested, although the relationship varies (very slightly in any case) with meteorological conditions, the fertility of the soil and certain other factors. As a general rule, a harvest of approximately 2 quintals of poppy seed is obtained from a cultivated area of 1 Hungarian hold (0.578 ha); on that basis, the quantity of poppy straw obtained is smaller by a few tenths of 1%. For example, in 1960, in Hungary, the quantity of poppy seed harvested per hold in a certain plot of land was of the order of 2.46 quintals (each capsule containing 3.53 g of seed), and the quantity of poppy straw harvested on the same land was 2.24 quintals per hold.

Control operates automatically in the following manner. At the time of the harvest, the purchasing agencies take samples of about 100 poppy capsules, with approximately 10 cm of straw attached, at various points in a given field; the ratio of the weight of seed to that of straw is calculated so as to determine the deliveries of poppy straw, which should correspond to a given quantity of seed. If the quantity of poppy straw delivered is less, the cultivator is required to replace the missing straw. It should also be added that, in Hungary, the poppy plant is grown exclusively for the purpose of obtaining the poppy seed and its oil, and that the sale of the poppy seed is becoming year by year more remunerative under the contracts entered into with the purchasing agencies. It is obvious that, in view of these advantageous conditions, practically the whole of the poppy seed and straw produced reaches the purchasing agencies, allowing for certain quantities of straw, which, as we have already stated, are used by cultivators as cattle bedding, or merely as fuel.

The foregoing procedure provides the equivalent of an absolutely safe control.

As soon as the poppy straw reaches the stores of the above-mentioned factory, the average morphine content of the various lots is determined, according to their origin and species. This method makes it possible to determine the yield in alkaloids of the various species of poppy selected.

Although the Hungarian People's Republic is a producer of poppy straw, addiction has not taken roots in the country, thus showing that the production of poppy straw does not of itself lead to any illicit use. Opium, on the other hand, is a narcotic drug par excellence; its morphine content can attain approximately 15% and opium can produce addiction by itself in the absence of any chemical conversion. Poppy straw cannot be considered as a narcotic drug, since it is a very bulky raw material with an average morphine content of barely 0.3% to 0.4%. From the foregoing it will be apparent that any attempt at clandestine manufacture of morphine from poppy straw would be much too dangerous for those wanting to engage in it, because the large volume of raw material to be processed would expose them to detection. No attempts to manufacture morphine illicitly in our country have come to our knowledge.

There is no extraction of alkaloids from the poppy straw outside the Alkaloïda factory, the staff of which consists of trustworthy specialists.

The Alkaloïda chemical products factory is required to register the following data on its factory journal: quantities of raw material processed; date and mode of transport to the factory; quantity of alkaloids produced; quantity delivered by the factory; date and mode of transport from the factory; losses in manufacture; and quantity of alkaloids used for pharmaceutical preparations.

The factory is required to prepare every three months a general table containing the above data and to submit it to the Hungarian control agency. In addition, the Public Health Office and the police authorities inspect the factory at least once every six months, and sometimes several times a year (19).

In the Hungarian People's Republic, the manufacture of these alkaloids and the control relating to their manufacture are governed by the provisions of decree No. 2222/1934 issued by the Hungarian Prime Minister to implement the International Opium Convention, signed at Geneva on 19 February 1925 (incorporated into Hungarian legislation under No. XXXVII/1930) and the international Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs, signed at Geneva on 13 July 1931 (incorporated into Hungarian legislation under No. XXXVIII/1933).

In any event, there is no problem of addiction in Hungary. The few cases of addiction observed have resulted from prolonged medical treatment of patients in a grave condition.

* * *

The Kabay process of Hungarian origin has given a great impetus to the manufacture of morphine during the past thirty years, not only in our country but also throughout the world; this process is preferred everywhere because it is economical, and because poppy straw cannot give rise to any abuse.

The improvement of technical methods and the increase in the morphine percentage yield will contribute to spread this method, and at the same time bring about a fall in the quantities of morphine manufactured from opium.

The author wishes to express his deep gratitude to Dr. I. Véertes, representative of the Hungarian People's Republic to the United Nations Commission on Narcotic Drugs, for valuable advice kindly given by him in the preparation of this paper; he also thanks the management of the Alkaloïda factory and, in particular, Dr. E. Alberovsky, for their kind assistance in preparing this paper. Lastly, the author wishes to thank Professor J. Halmai for supplying him with important information on the life of János Kabay.

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Human pharmacology and addictiveness of ethyl 1-(3-cyano-3, 3-phenylpropyl)-4-phenyl-4-piperidine carboxylate hydrochloride (R-1132, Diphenoxylate)

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This drug, hereinafter designated R-1132, is a congener of meperidine, and was developed by Janssen & Jageneau (1). It has pronounced constipating and antidiarrheoal properties in mice, rats, dogs, cats, rabbits, and guinea pigs (2), and in man (3), small doses orally (2.5-5 mg several times a day with a maximum total of 30 mg daily for adults) are effective for this purpose. It does not possess analgesic activity for mice or rats by subcutaneous injection, and the constipating activity is not antagonized by nalorphine (2).

Thus it appears that, at least in animals, a disssociation between two of the characteristic actions of opiate-like drugs (analgesic and constipative effects) has been achieved with the synthesis of R-1132. This suggested the possibility that R-1132 might also differ from other opiate-like antidiarrhoeal agents with respect to addiction liability, and that, if the latter were significantly less, R-1132 might be used to advantage when an opiate-like drug is indicated in the control of diarrhoea. Therefore, the human addiction liability of R-1132, relative to that of morphine and codeine, was evaluated in a series of experiments with emphasis on the oral route of administration of these drugs.

General methodology

The subjects used in these studies were healthy adult white or negro males with previous histories of opiate addiction of long duration, who were serving sentences for violation of state or federal narcotic laws, and who volunteered for the experiment.

The tests employed included the following procedures: (i) administration of single graded doses for the detection of morphine-like subjective (euphorogenic) effects and/or morphine-like behaviour, (ii) substitution of R-1132 orally for morphine, in relatively large doses for 24 hours or 10 days, in patients addicted to morphine to ascertain its effectiveness in preventing symptoms of abstinence, (iii) " direct addiction ", which involved administration of these drugs in high or else progressively increasing doses as tolerated for 5, 18 or 60 days, followed by abrupt withdrawal to ascertain the presence and degree of physical dependence, and (iv) an attempt to precipitate abstinence phenomena by administration of nalorphine subcutaneously after 30 to 40 days of chronic intoxication with R-1132. For convenience in presentation, the specific details of methods and results will be described for each experiment.

Detailed methods and results

Experiment 1

Effects of single oral doses (2-20 mg) of R-1132 in non-tolerant patients

Methods. In a preliminary study using seven patients, it was ascertained that in a dose range of 2-20 mg the effects of R-1132 could not be distinguished from those of a placebo. A cross-over experiment, using ten patients, was then set up to compare more quantitatively the effects of R-1132 (20 mg/80 kg) with those of morphine (20 mg/80 kg) and a placebo, employing the method of Fraser *et al* (4). Three conditions were used: (i) R-1132 orally plus a subcutaneous placebo, (ii) an oral placebo plus morphine sulfate subcutaneously; and (iii) an oral and subcutaneous placebo. Two pre-drug and several post-drug observations were made at hourly intervals for seven successive hours. Measurements included rectal temperature, respiratory rate, respiratory minute volume, diameter of pupil, pulse rate and blood pressure. Patients were questioned concerning the subjective effects induced by the drug, and were observed for signs of morphine-like intoxication, including the incidence of vomiting. Differences between drugs were evaluated by the paired *t*-test.

Results. After R-1132 orally plus a placebo subcutaneously no opiate-like subjective effects were reported, and no opiate-like changes in behaviour were observed. In these doses, the effects of R-1132 on the variables measured were not significantly different from those of a placebo. After morphine subcutaneously plus an oral placebo, characteristic morphine-like effects developed.

Experiment 2

Effects of single oral doses of R-1132 (40-60 mg) as compared with codeine (60-90 mg) and morphine (20-30 mg)

Methods. This was a double-blind experiment in which 14 non-tolerant former opiate addicts served as subjects. Identically appearing capsules were administered at 7.30 a.m. while patients were fasting. All subjects received at weekly intervals in a randomized order the following medications: placebo capsules; morphine sulfate, 20 and 30 mg; codeine sulfate, 60 and 90 mg; and R-1132, 40 and 60 mg.

Observations were made immediately before, and one, two, three, four, six, eight, ten, twelve and fourteen hours after administration of the capsules.

TABLE 1

Subjective effects of morphine, codeine and R-1132 given orally

Drug	Dose (mg)	Number of patients (of 14) responding [a]				Average [b] total responses
		Positive, opiates	Positive, other drug	Question-able	Negative	
Placebo ...	—	1	[1][c]	1	12	1.4
Morphine .	20	7	1 [1]	3	3	11.1
Morphine .	30	7	2	3	2	11.9
Codeine...	60	5	1 [1]	4	4	6.0
Codeine...	90	6	1	5	2	9.5
R-1132 ...	40	4	2 [1]	5	3	11.1
R-1132 ...	60	11	1 [1]	2	0	16.9

[a] For method of scoring, see reference No. 5.

[b] See reference No. 5 for method of obtaining these figures.

[c] Figures in brackets represent patients who also reported positively for opiates.

At these times, both patients and aides completed a questionnaire designed to quantify both the subjective effects of the drugs as reported by the patients, and the changes in behaviour as observed by the aides (5). The data obtained with this questionnaire were analysed as previously described (5).

Results. The data on the subjective effects of morphine, codeine and R-1132 are summarized in table 1. It is noteworthy that eleven of the fourteen patients reported the subjective effects of 60 mg of R-1132 were opiate-like, whereas only seven of fourteen so reported after 90 mg of codeine. As judged by this criterion, 60 mg of R-1132 orally is a more effective "euphoriant" than 30 mg of morphine or 90 mg of codeine. The negligible response to placebo should also be noted. Although good dose-effect curves were not obtained (table 1), it appears that R-1132 is roughly one-half as potent as morphine in this respect, and is roughly 1.5 times as potent as codeine.

Experiment 3

Effects of three successive "euphorogenic" doses of R-1132 and codeine administered orally at weekly intervals, and precipitation of abstinence with nalorphine

Methods. The purposes of this experiment were: (i) to ascertain if tolerance developed when R-1132 or codeine was administered in a euphorogenic dose once weekly for three successive weeks, and (ii) to determine the relative potency of single oral doses of R-1132 and codeine, utilizing a new subjective questionnaire for patients and a parallel, but separate, behaviour questionnaire for observers.

Eight non-tolerant patients were used in a double-blind test as follows: At weekly intervals, four subjects received three identical oral doses of codeine phosphate (140 mg), a placebo on the fourth week, followed by three successive weekly doses of 70 mg of R-1132. The other four patients received the same dosages of drugs with the sequence reversed. One week after each patient received his last dose of drug, each was given 10 mg of nalorphine subcutaneously (4) (latter was studied, because in monkeys (6) nalorphine-precipitated abstinence could be demonstrated as long as two or three weeks after the subcutaneous injection of one very large dose of R-1132).

Observations made were immediately before and one, two, three, four, six, eight, ten, twelve and fourteen hours after administration of the capsules at 7.30 a.m. At these times the patients completed a "single dose attitude" questionnaire for opiates (patients' ratings) consisting of the following: "Do you feel the medicine?" "This drug is most like what drug listed below (check one): a blank, dope (opiates), cocaine, marihuana, goof balls (barbiturates), benzedrine ("benny"), other"; "Check each sensation which you feel: normal, turning of the stomach,* skin itchy,* relaxed,* coasting,* soap-box,* pleasant sick,* sleepy, drive,* nervous, drunken, other"; "My liking for this drug is most nearly described by which of the following: not at all, slight, moderate, a lot, an awful lot, other", and "Comments". Responses to the question respecting degree of "liking for the drug" were graded on a weighted basis from 0 for "not at all", to 4 for "an awful lot," hence the minimum score for nine observations would be 0, and the maximum score 36. Symptoms marked with an asterisk were classified as specific for opiates, while other symptoms were considered to be relatively non-specific, since they are frequently reported after administration of drugs of other classes (e.g., barbiturates, alcohol, amphetamine).

For purposes of presentation, responses relating to the "specific" subjective and behavioural effects of the three drugs and placebo were classified under three headings: (i) identification as "dope" (opiates), (ii) incidence of opiate symptoms, and (iii) a weighted "attitude" score, representing the over-all preference for or aversion to each of the medications.

Concurrently and independently the observers completed the parallel questionnaire in which drugs were evaluated on the basis of the patient's behaviour. In addition, the diameter of the pupils in a controlled lighted room was recorded as in the previous experiment.

Both patients and aides were instructed to check *only* items observed since the last hourly observations, and if the words listed were not satisfactory, to insert others considered more appropriate or to make comments.

Results. When the results of the 8 subjects were averaged there was no significant change in successive weeks for either R-1132 (70 mg) or codeine (140 mg), indicating that on this regimen no significant tolerance to these effects developed. The total response curves (TRS) for the entire 14 hours for these variables are shown in figure 1. The TRS values for positive attitude scores and the incidence of opiate symptoms are similar for R-1132 and codeine. The TRS values for identification as "dope" are greater, but not significantly so for R-1132 as compared with codeine. These values are consistently low for a placebo, and none of the subjects at any time identified the placebo as "dope". With these doses

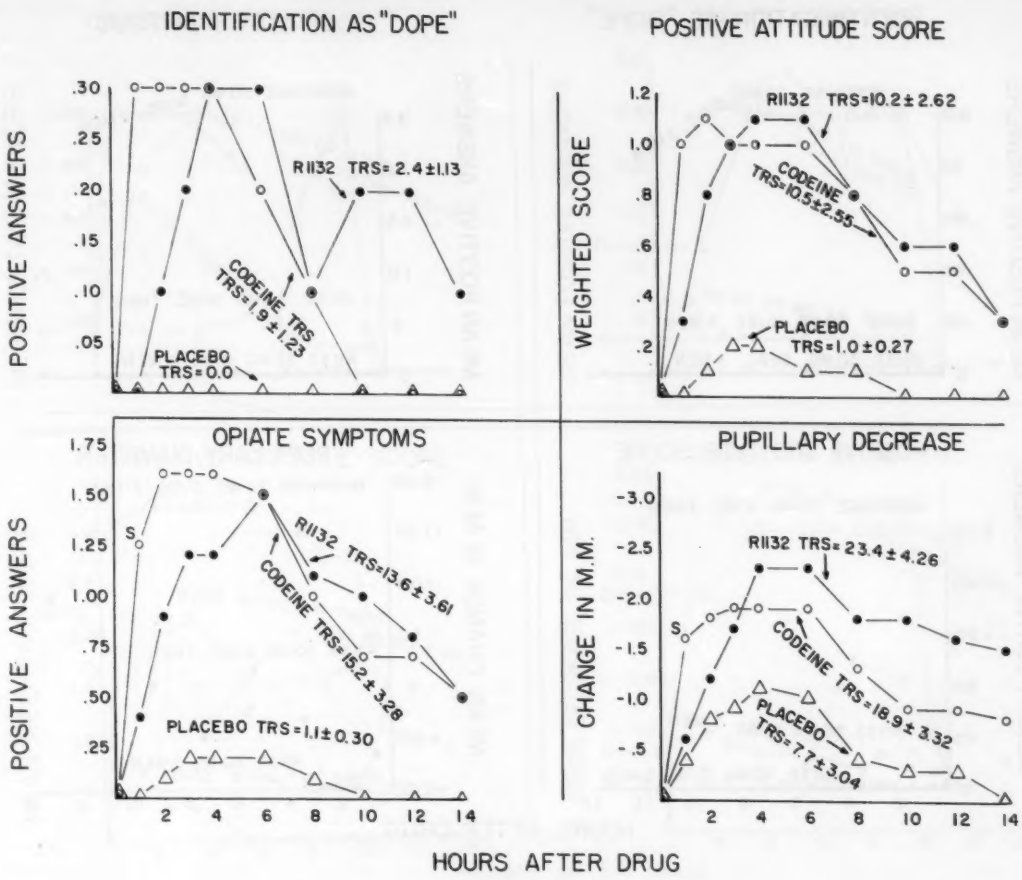

FIGURE 1

Effects of single oral doses of R-1132 (70 mg), codeine (140 mg) and a placebo respecting (i) *identification as dope (maximum number of positive answers hourly = 1);* (ii) *incidence of opiate symptoms (maximum possible positive answers hourly = 7.0);* (iii) *attitude score (maximum possible hourly score = 4.0); and* (iv) *decrease in pupillary diameter. Each point on each curve represents the average of data obtained on eight men, each of whom had R-1132 and codeine three times and a placebo once. "TRS" values represent the mean areas (total response scores for 14 hours) ± standard areas of the means. The letter "S" on the codeine curve indicates that this point is significantly different from a corresponding point on the R-1132 curve, and illustrates the more rapid onset of effects of codeine as compared to those of R-1132.*

of R-1132 and codeine, the peak value for all measurements is similar. The outstanding difference between R-1132 and codeine is in the time course. Peak effects of codeine were registered in every instance one to two hours after medication, whereas peak effects of R-1132 were from four to six hours after medication; the difference was statistically significant at the end of the first hour in the case of opiate symptoms and pupillary diameter. As noted in figure 1, the effects of R-1132 persisted longer than did those of codeine. When 10 mg of nalorphine was given one week after the last dose of codeine or R-1132, only the anticipated nalorphine effects *per se* and no signs of abstinence were observed. The results of this experiment confirmed those of the previous one on the comparative effects of single doses of R-1132 and codeine, and, in addition, they suggest that the relative potency of R-1132 may be somewhat greater than that indicated in experiment 2.

Experiment 4

Effects of single subcutaneous doses of R-1132

Methods. R-1132 is extremely insoluble in water and most organic solvents, and for these tests it was necessary to dissolve it in pure propylene glycol and administer with a dry syringe. In a preliminary study, doses in the therapeutic range (2-15 mg) induced no detectable effects in ten tests using non-tolerant former opiate addicts. Higher doses were

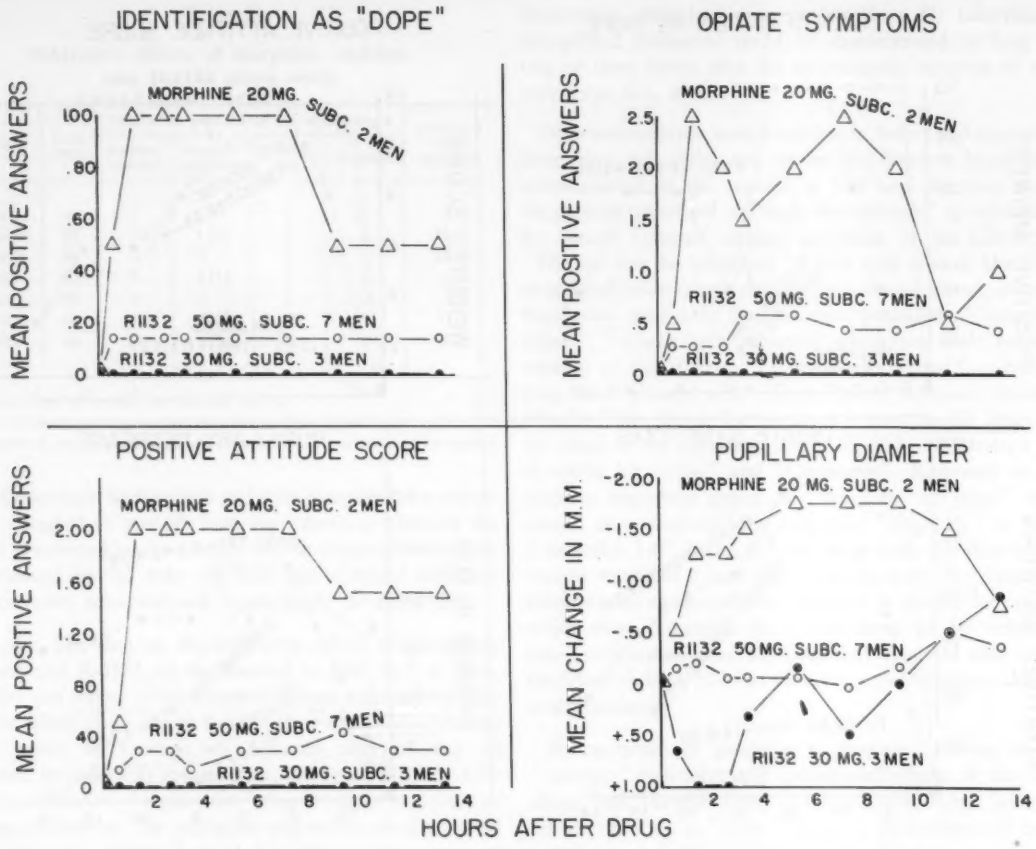

FIGURE 2

Average effects of single subcutaneous doses of R-1132 (30 and 50 mg) and of morphine sulfate (20 mg). All drugs were dissolved in pure propylene glycol.

therefore given as follows: 30 mg (3 patients) and 50 mg (7 patients). Observations were made at intervals as described in experiment 3. In order to ɐɲɹ out interfering effects of the vehicle, two patients were given 20 mg of morphine sulfate dissolved in pure propylene glycol and similarly observed. In addition, an attempt was made to precipitate abstinence phenomena with 10 mg of nalorphine in three patients: in one, four days, and in two, six days after they received single doses of R-1132 (50 mg).

Results. In doses of 2-15 mg (ten tests) and even in a dose of 30 mg (three tests), R-1132 induced no detectable effects, but in a dose of 50 mg, minimal effects were observed (figure 2). On the other hand, when 20 mg of morphine was dissolved in propylene glycol and injected subcutaneously, a complete pattern of morphine effects developed (figure 2). After nalorphine, no abstinence phenomena were precipitated.

Experiment 5

Effects of single intravenous doses of R-1132

Methods. In a preliminary study, doses of 5, 10 and 15 mg of R-1132 dissolved in pure propylene glycol provoked no definite effects in three tests on non-tolerant subjects. Higher doses were therefore given as follows: 30 mg (three patients) and 50 mg (seven patients). Observations were made at intervals, as described in experiment 3.

Results. In doses of 30 mg, R-1132 produced mild but definite opiate-like effects, and when the dosage was increased to 50 mg very definite and characteristic symptoms of morphine-like intoxication were observed (figure 3). The principal difference between R-1132 intravenously and heroin or morphine was that the onset of effects after R-1132 was very gradual and no definite identification of opiate-like

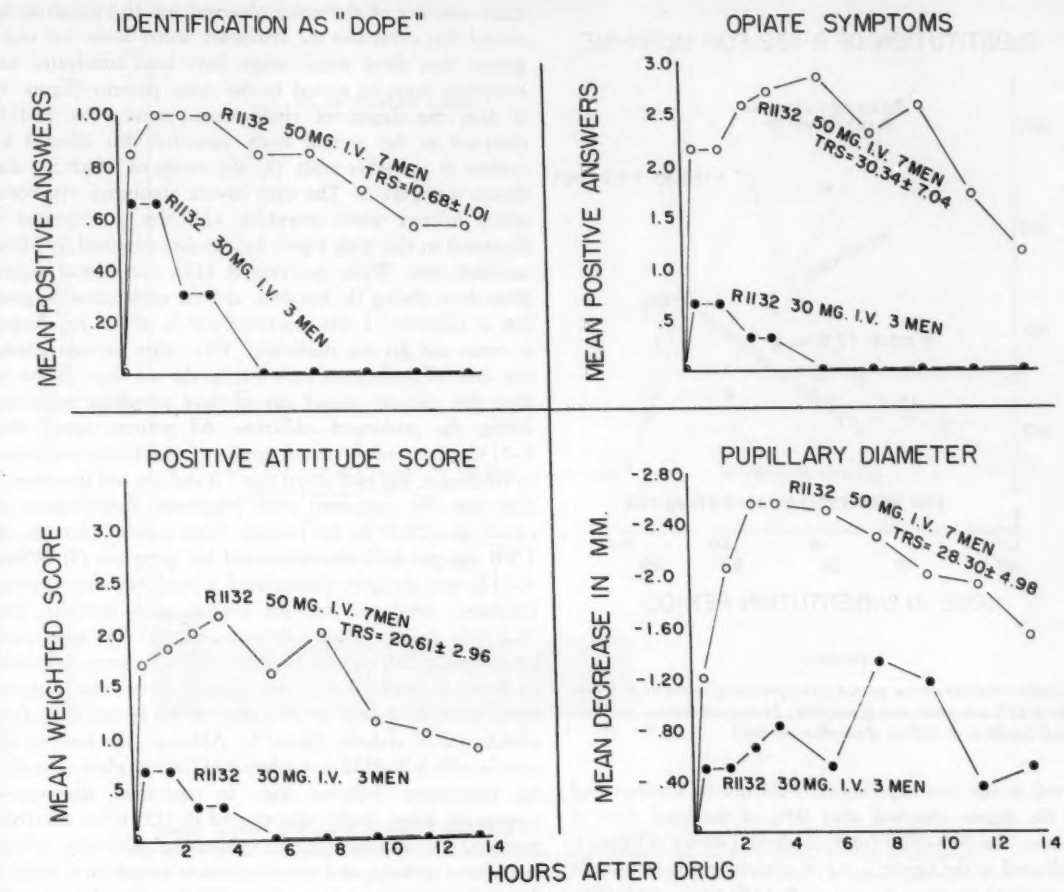

FIGURE 3

Average effects of single intravenous doses of 30 and 50 mg of R-1132 (dissolved in propylene glycol). "TRS" values represent the mean areas (total response scores for 14 hours) ± standard errors of the means.

effects were made until about 10 to 20 minutes after injection; however, after 30 minutes the effects were pronounced (figure 3).

Although not presented in the figure, the changes in behaviour recorded by the aides corresponded closely to those reported by the patients, and both of these paralleled the changes observed in pupillary diameter with respect to both time course and intensity of effect (figure 3).

Experiment 6

Suppression of abstinence for 24 hours

Methods. Two different experiments were done at different times. In the first, ten patients who had been stabilized on an average of 240 mg of morphine sulfate subcutaneously daily received 150 to 200 mg of R-1132 (average 182 mg), divided into four or five oral doses, during the 24-hour substitution period. In the second experiment, five patients who were addicted to and stabilized on 240 mg of morphine sulfate daily received 30 mg of R-1132, six, fourteen and eighteen hours after their last dose of morphine (total dose during the substitution period being 90 mg). For comparison, data were available on nine patients (all of whom received R-1132 in the first substitution experiment) who received on three separate occasions 18, 36 and 90 mg of morphine (10, 20 and 50 per cent of their accustomed dose of morphine) during similar 24-hour substitution tests (5).

Dose effect curves were constructed from the mean point-hour scores after two dose levels of R-1132, and three dose levels of morphine. Regression lines, relative potencies, and 95% confidence limits were calculated according to the method of Bliss (7).

Results. R-1132 proved to be an effective supressor of abstinence from morphine. The degree of suppression

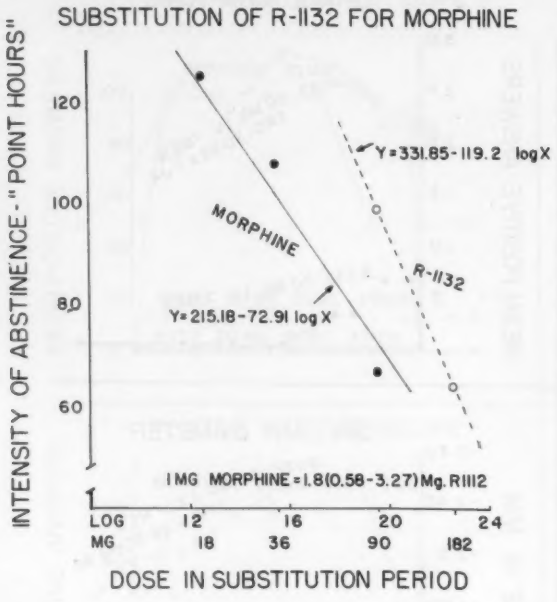

FIGURE 4

Dose-effect curves and relative potency for suppression of abstinence from morphine by R-1132 and graded doses of morphine; 24-hour substitutions in addicted individuals stabilized on 240 mg of morphine per day.

observed in the first experiment could not be distinguished from the degree observed after 50% of the usual dose of morphine. The dose-effect curve obtained is shown in figure 4. As indicated in the figure, 1 mg of morphine subcutaneously was calculated to equal 1.8 mg of R-1132 orally, with 95% confidence limits of 0.58-3.27 mg with respect to potency in suppressing abstinence from morphine.*

Experiment 7

Substitution of R-1132 for morphine for ten days, followed by abrupt withdrawal of R-1132

Methods. This was evaluated in five patients, each of whom had been stabilized on 240 mg of morphine sulfate daily, and had been addicted for 107, 153, 188, 189 and 201 days. Morphine was abruptly discontinued in all patients and replaced by 180 mg of R-1132 divided in approximately four equal doses daily. After ten days of substitution, R-1132 was abruptly discontinued and no therapy given. Intensity of abstinence was measured by the daily point score of Kolb & Himmelsbach (8).

Results. R-1132 suppressed symptoms of abstinence from morphine very satisfactorily, but not completely. The maximum intensity of abstinence observed was 10.5 points on the second day, otherwise the abstinence scores were not much greater than those which might have been anticipated had morphine been continued in the same patients (figure 5). In fact, the degree of abstinence-suppression by R-1132 observed in the present study exceeded that effected by codeine in an earlier study (9), the results of which are also shown in figure 5. The very severe abstinence syndrome which follows when morphine addiction is untreated is illustrated in this same figure by the data obtained by Himmelsbach (10). While receiving R-1132, one subject missed three doses during the ten days, and the explanation he gave was as follows: "I was practicing my horn and just forgot to come and get my medicine." Two other patients missed one dose of medication each during the ten days. None of these five patients missed any of their morphine injections during the prolonged addiction. All patients stated that R-1132 prevented the development of significant symptoms of abstinence, but each stated that "it did not feel like dope." This may be contrasted with consistent identification of opiate-like effects by the patients when codeine (average of 1,500 mg per day) was substituted for morphine (9). When R-1132 was abruptly discontinued a mild but characteristic syndrome developed and the average peak intensity was 18.2 daily points. When codeine (1,500 mg) was substituted for morphine (260 mg) for 14 days in the experiment described by Fraser & Isbell (9) there was a much greater rise in abstinence scores to a peak of 34 points on the second day after withdrawal of codeine (figure 5). Although the number of cases in which R-1132 was substituted for morphine is small, the experiment indicates that, in equivalent abstinence-suppressing doses, orally administered R-1132 is less effective than codeine in producing morphine-like subjective effects in addicted patients, and that it produces less physical dependence than codeine after substitution for morphine for a period of ten days.

Experiment 8

"Long" direct addiction to R-1132 (orally)

Methods. This was evaluated in five initially non-tolerant subjects who were addicted from 45 to 61 days in a dosage outlined in table 2. The usual plan in such experiments is to increase the dose of the drug as rapidly as possible during the first 18 days of addiction, and then to continue medication at the dosage attained for an additional 40 to 70 days. However, since uncomfortable gastro-intestinal complications might occur on such a schedule in the case of R-1132, the dosage of this drug was increased much more gradually than is usually the case, using as a guide its effectiveness in causing constipation and the absence of toxic symptoms. In order to obtain data on the frequency of stools and necessary laboratory data, all subjects were examined for a considerable time without drugs. Observations during pre-drug, medication, and withdrawal phases included weight and caloric intake daily, and temperature, pulse, respiratory rate and blood pressure three times daily. Special observations included number of stools daily, hours of sleep, hours of inactivity,

* In corresponding substitution tests, it was ascertained that 1 mg morphine subcutaneously is equivalent to 2.86 mg of morphine orally, and to 13.7 mg of codeine orally (unpublished data of Fraser, Wolbach & Martin).

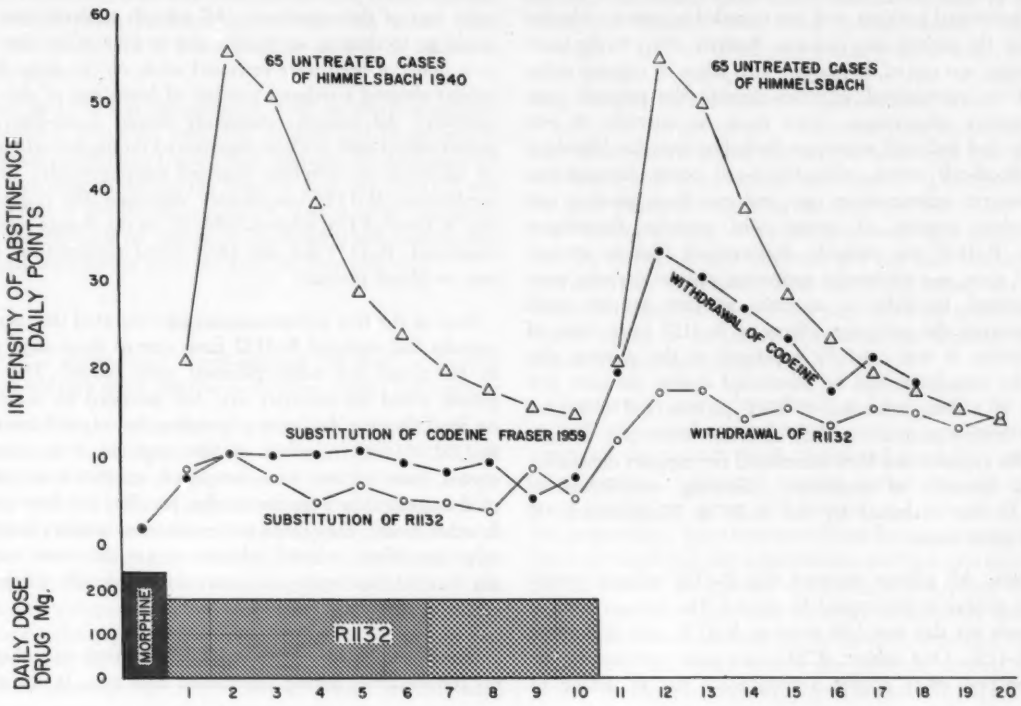

FIGURE 5

Average intensity of abstinence recorded in daily point scores of five patients while stabilized on 240 mg of morphine daily; when morphine was discontinued and R-1132 substituted in an average dosage of 180 mg daily; and the intensity of abstinence when R-1132 was discontinued abruptly. These scores are compared with the average scores of ten subjects in another experiment (Fraser & Isbell), when codeine was substituted for morphine and when codeine was withdrawn. These are also compared with the intensity of abstinence in 65 untreated cases reported by Himmelsbach.

TABLE 2

Direct addiction to R-1132, comparison of observations during pre-drug or control, addiction and withdrawal

Subject	Days		Daily dose		Wt. last day		Resp./Min.			Hours sleep			Hours inactive			Hours active			Average daily stools	
	Pre-drug	R-1132	Initial	Maximum	Pre-drug	R-1132	Pre-drug	R-1132	Withdrawal	Pre-drug	R-1132	Withdrawal	Pre-drug	R-1132	Withdrawal	Pre-drug	R-1132	Withdrawal	Pre-drug	R-1132
			(mg)	(mg)	(kg)	(kg)														
CEP	33	59	45	285	65.60	69.65	16	15	15	7.75	8.26	7.00	11.76	11.90	8.06	5.00	2.32[a]	4.95	1.42	1.07[a]
SIM.....	39	59	50	215	95.68	98.20	23	19[a]	19	7.15	4.50	9.35	10.76	8.00	12.55	2.48	0.87[a]	2.75	0.95	0.61[a]
MOO	35	45	50	155	62.90	63.22	22	22	24	7.80	8.13	5.30	10.55	11.60	10.05	3.75	2.72[a]	4.35	0.86	0.21[a]
RIC.....	14[b]	60	20	105	56.80	59.00	18	15[a]	19	5.71	6.75	6.45	9.00	11.00	10.20	1.75	1.27[a]	2.35	1.07	0.47[a]
WAS.....	24	61	45	180	84.90	82.30	19	16[a]	18	6.77	7.99[a]	7.40	10.60	11.30	11.15	6.52	4.12[a]	5.60	1.00	0.56[a]
Average ..	29	57	42	188	73.18	74.47	19.6	17.4	19	7.04	7.13	7.10	10.53	10.76	10.40	3.90	2.26	4.00	1.06	0.58

[a] Significantly different (0.05) as compared with control observations; computations were made using the same individual as his own control.

[b] Post-drug, tenth to twenty-fourth day after R-1132 discontinued.

and hours of activity, all of which were recorded at half-hour intervals daily. Inactivity refers to hours spent on bed in a horizontal position, and was recorded as positive whether or not the patient was sleeping. Activity refers to the hours a patient was out of the ward — i.e., when he pursued either work or recreational activities outside the research unit. Laboratory observations were made at intervals of two weeks and included urinalyses (including tests for bilirubin), red-blood-cell count, white-blood-cell count, hemoglobin, hematocrit, sedimentation rate, and two liver function tests (bilirubin content of serum and cephalin flocculation tests). R-1132 was abruptly discontinued after an average of 57 days, and identically appearing placebo capsules were substituted. In order to ascertain whether patients could differentiate the subjective effects of R-1132 from those of a placebo, it was carefully explained to the patients that placebo capsules would be substituted during the next few days, at a time unknown to both patients and observers. They were requested to notify observers when they thought placebo capsules had been substituted for capsules containing drugs. Intensity of abstinence following withdrawal of R-1132 was evaluated by the Kolb & Himmelsbach (8) daily point score.

Results. All subjects reported that R-1132 induced constipation similar to that caused by opiates. The average number of stools per day was 1.06 prior to R-1132, and 0.58 while on R-1132. One subject (CEP) was quite resistant to the constipating effect despite a progressive rise in dosage to 285 mg of R-1132 daily (table 1). One subject (RIC) reported some difficulty in urination and occasional nausea during the early part of the experiment. All subjects reported that they could go to sleep more readily, and in four of the five subjects hours of sleep were increased while on the drug. Every subject showed a reduced number of hours out of the ward (activity). All subjects consistently denied opiate-like, subjective effects such as those experienced during the early phases of addiction to morphine (injected subcutaneously) or oral methadone. R-1132 significantly depressed the respiratory rate in three of five subjects (table 2). In the dosage schedule employed, R-1132 did not affect rectal temperature, pulse rate or blood pressure.

Four of the five patients erroneously reported that placebo capsules had replaced R-1132 from one to three days prior to the actual day when placebos were started. The fifth patient stated the incorrect day, but amended his statement on the following day, correctly stating he was still receiving R-1132. However, when placebo capsules were actually started, four patients who developed significant symptoms of abstinence then were certain that placebos had been given. In other words, they could not evaluate accurately, from the subjective effects induced, whether or not they were receiving R-1132, but were able correctly to identify subjective effects of abstinence from R-1132.

Urinalyses, blood counts and liver function tests showed no abnormalities during maintained addiction. In the three

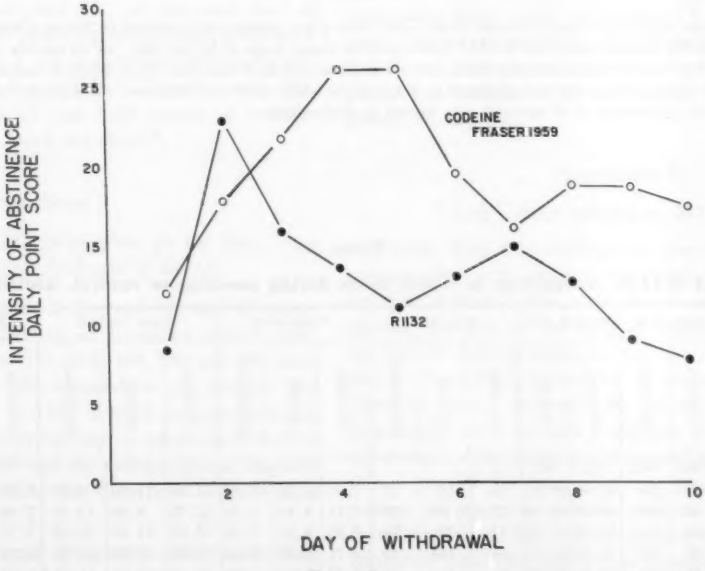

FIGURE 6

Average intensity of abstinence (daily point scores) of five patients when R-1132 was discontinued abruptly after 45 to 61 days of chronic administration. The average maximum dose maintained was 188 mg daily. These scores are compared with the average scores of eight men in another experiment, who were chronically maintained on an average of 1,550 mg of codeine daily, and after 60 days the codeine was withdrawn abruptly (11).

subjects tested for precipitation of abstinence with nalorphine, a positive result was recorded in every case, but this was considered to be somewhat milder than would have been anticipated for a corresponding period of addiction to morphine.

After R-1132 was discontinued, four of the five subjects developed a relatively mild, but definite and characteristic, abstinence syndrome. The average intensity of abstinence for these five subjects during the first ten days after R-1132 was withdrawn is illustrated in figure 6, and may be compared with the intensity of abstinence observed when codeine was abruptly withdrawn after 60 days of addiction (11).

Experiment 9

" Short," " double-blind," direct addiction (18 days) to R-1132 as compared with direct addiction to morphine, codeine and a placebo

Methods. Eight non-tolerant subjects were used, each to be exposed to all drugs. Three of these, CEP, WAS and MOO, were subjects in the previous study of chronic intoxication with R-1132. Morphine sulfate and codeine sulfate served as positive controls and starch capsules, flavoured with quinine, were the negative control. Four other drugs were included in this test, but they are not pertinent to this study (12). Each drug except the placebo was given orally in progressively increasing dosage, starting on the first day with a dosage one to two times the " maximal therapeutic " dosage, and ending on the eighteenth day with a dosage which approximated seven to ten times the initial dosage. The dose attained on the eighteenth day was given each patient on the nineteenth or twentieth day.

All drugs were discontinued in a randomized order on the eighteenth, nineteenth or twentieth day, and each was replaced with a placebo given at the usual time and in the usual form, quantity, and customary volume. After ten days of abstinence, each patient received another drug in the sequence.

The initial daily dosage of morphine was 32 mg, and the maximum dosage attained was 240 mg daily. Codeine was started with a dosage of 200 mg daily, and was increased to a maximum of 1,500 mg per day. No difficulty was encountered in increasing the dosage of either to these levels in any patient. The starting dose of R-1132 and the maximum attained varied (see table 3).

Observations and laboratory tests were the same as those made in the " long " addiction test, except that no record was kept of the number of stools passed.

The attitude of the patients toward the drugs administered was ascertained daily at 7 p.m. by the responses to a special " chronic dosage attitude " questionnaire for opiates (patients' ratings), which each completed without assistance. The questions asked were as follows: " Has this drug produced any effect on you? " " Does this drug feel like an opiate (dope)? " " If so, is it most like: heroin, morphine, codeine, other dope-like drug (please name); " and its " strength " is: " no effect, very weak, weak, average, strong, very strong, overdose; " or " is the feeling from this drug like one of the drugs given below: a blank (water), marihuana (reefer), cocaine, barbiturates (goof balls), alcohol (whiskey or beer), benzedrine (benny), other drug (please name); " and its " strength " is: " no effect, very weak, weak, average, strong, very strong, overdose; " " Would you like to take this drug every day? " Alternative answers listed were: " Yes," " No," and " Don't care. " " Does this drug make you feel bad? If so, does it make you feel so badly that you would stop taking it if you were not on a test? " " Describe briefly the most important effects of the drug ou you; " and " Are you ' kicking a habit '? " It was impressed upon the patients that the physicians and observers did not care whether the patients liked, disliked or were indifferent about any particular drug, and that the primary purpose of the questionnaire was to obtain as accurately as possible the attitude of the *patient* toward each drug.

Concurrently and independently at 7 p.m. daily, the aides, each of whom had a minimum of six years' continuous experience on the research ward, completed a parallel " attitude questionnaire " (observers' ratings), except that the queries were couched in terms of behaviour; for example, " Does this patient show behaviour resembling that seen after opiates? " Prior to completing the questionnaire, each aide was instructed not to consult the current questionnaire completed by the patient, but he could review the notes of any other observer, could take into consideration the opinion expressed by any other aide, and could review the previous answers of the patient to the questionnaire. He was instructed specifically, however, *not to hesitate to give his opinion of the effect of the drugs, even though it might be different from that of the subject.*

For purposes of presentation, the ratings of both patients and aides were classified under four general headings: (i) any drug effect, (ii) identified as " dope " (or behaviour like after " dope "), estimate of " strength of drug " (or estimate of potency), and (iv) " would like to take daily? " and scores were computed on the basis of frequency of response.

Results. Each of the eight patients completed the entire test on all drugs, except one patient, who quit the test after having received seven of the eight drugs, stating that the " drive " while on drugs was insufficient to compensate for the degree

TABLE 3

Daily dosage of R-1132
"Short" direct addiction test

Subject	Days on drug	Initial dose (mg)	Maximum dose (mg)	Total dose (mg)
GR	20	40	300	3,300
CEP	20	40	300	3,320
WA	19	64	480	4,954
WAS	18	40	300	2,720
MOO	19	64	480	4,954
BR	19	40	160	2,320
SU	20	60	400	4,890

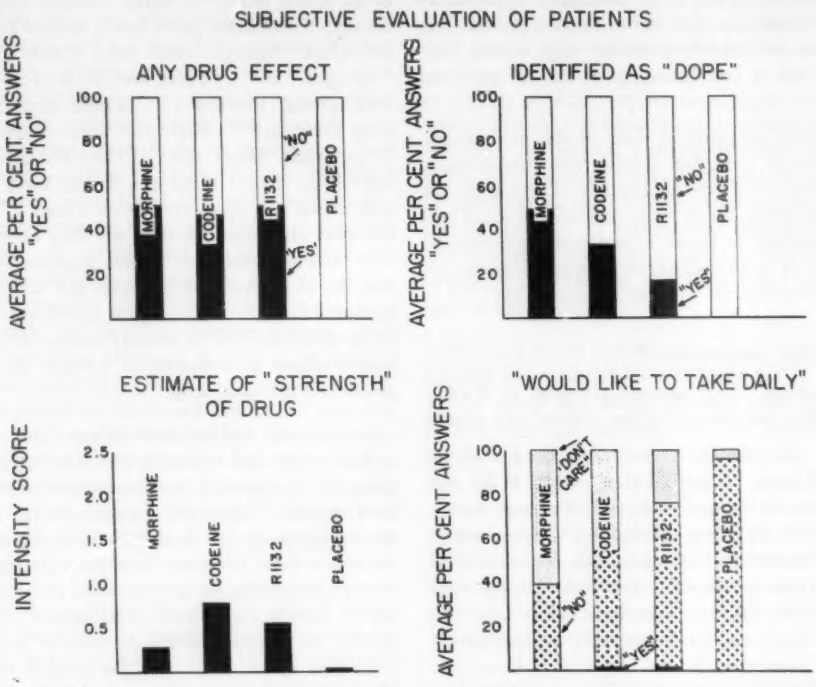

FIGURE 7*a*

Summary of "subjective" evaluation by patients, tabulated from patients' questionnaires during the 18-20-day "double-blind" study (experiment 9), when they received orally in an accelerating dosage, morphine, codeine, R-1132 and a placebo.

of abstinence which developed. It happened that R-1132 was the eighth drug which this patient was scheduled to take, and hence only seven patients received R-1132 chronically during this study. In the case of morphine and codeine, no difficulty was encountered in progressively raising the dosage according to plan. However, in the case of one patient receiving R-1132, the dosage was progressively elevated to 160 mg by the eleventh day, but the patient became so sedated (spending 18 to 22 hours horizontal in his bed daily) that it was decided not to increase the dosage further until the patient showed some significant evidence of tolerance. Since he continued to be highly sedated, no further attempt was made to augment his dosage during the remainder of the test.

While receiving medication, all these patients showed constriction of the pupils, considerable sedation, constipation, and some pruritus. There was also nausea in several patients, but neither nausea nor vomiting was conspicuous, despite this progressive increase in dosage.

The average effects of R-1132, codeine and morphine as compared with those of a placebo on respiratory rate, systolic blood pressure, rectal temperature, hours of sleep, hours of activity, and hours of inactivity are shown in table 4. It is apparent that all of these drugs depressed respiratory rate significantly to approximately equal degrees, and tended to increase inactivity. None of the drugs affected significantly systolic blood pressure, rectal temperature, hours of sleep per day, or initiative activity. The results obtained with the questionnaires (figures 7 *a* and 7 *b*) represent average responses on a percentage basis from the total of 134 in the case of R-1132 (N = 7), and 154 in the case of morphine, codeine and pla-

TABLE 4

Average daily effects of drugs as compared with a placebo on certain physiological measurements for all subjects during the first 18 days of medication

Drug	Resp. rate	Systolic B/P	Rectal temp., °C	Sleep hours	Activity hours	Inactivity hours
Placebo[a]	18.8	109.7	37.03	7.08	3.34	10.35
R-1132	14.6[b]	105.8	37.08	7.74	2.79	12.50[c]
Codeine	14.5[b]	107.6	36.96	6.88	3.93	11.23
Morphine ...	15.1[b]	106.3	37.00	7.16	3.15	11.00

[a] Each patient was on a placebo for 30 consecutive days, but his tabulation covers only the first 20 days on placebo.

[b] Value is significantly different from that observed when a placebo is given. The paired "t" value comparing R-1132 and a placebo is 6.20; comparing codeine with a placebo is 6.00; and comparing morphine with a palcebo is 10.6.

[c] Value is significantly different from that observed when a placebo is given; "t" = 2.55.

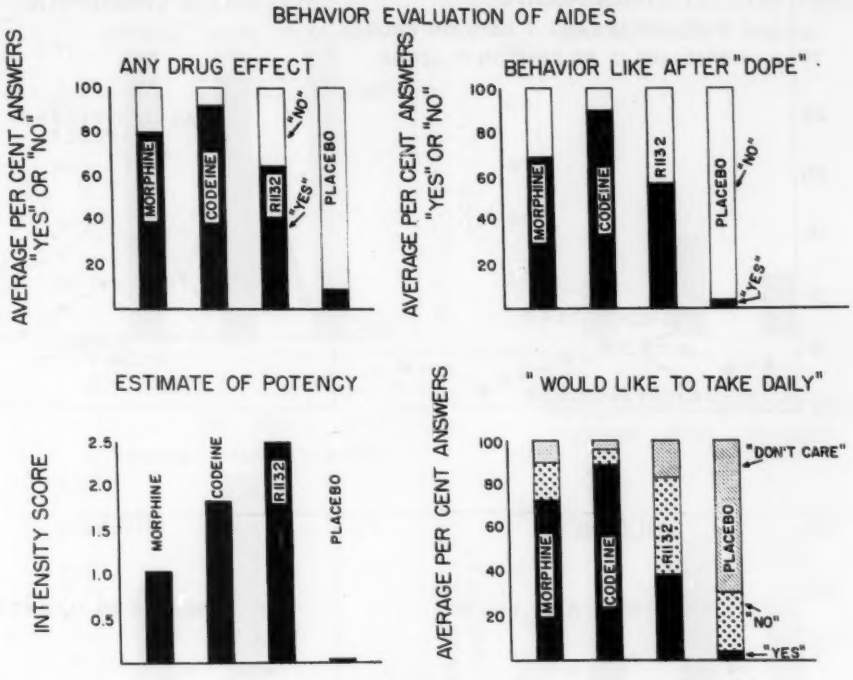

FIGURE 7 *b*

Summary of results of questionnaires prepared by aides when they evaluated the effects of morphine, codeine, R-1132, and a placebo on the basis of the patients' behaviour during the 18-20-day " double-blind " direct addiction study (experiment 9).

cebo (N = 8). Patients recognized some drug effect about 50% of the time when morphine, codeine and R-1132 were given. It is remarkable, since the study was conducted " double-blind ", that in no instance did the patients state a placebo produced any drug effect.

Although aides considered that all drugs possessed opiate characteristics to quite a high degree, it would appear that both patients and aides thought R-1132 was less opiate-like than morphine and codeine. In fact, patients were much more impressed by the sedative characteristics of R-1132 than its opiate qualities. For example, one patient (MOO), who contributed 70% of the " yes " answers to the question, " feels like opiates (dope) " (figure 7*a*), positively identified R-1132 in the non-opiate category concurrently, and in response to the question, " type of dope ", he wrote in " goof balls " (barbiturates) every time.

Intensity of abstinence, as indicated by the daily point and TAS-10 scores, is shown for morphine, codeine and R-1132 in figure 8. These were compared with the intensity of abstinence observed when a placebo was the " drug of addiction ". Intensity of abstinence after withdrawal of R-1132 was only slightly less than that observed after withdrawal of codeine, but significantly less severe than that observed after withdrawal of morphine ($P = < 0.001$). The over-all pattern of withdrawal from R-1132 and codeine was similar, and the abstinence syndrome in each instance was mild. Intensity of abstinence as previously described was computed by two procedures: the standard procedure of Himmelsbach, using as a baseline the last seven days on drug, and a modified procedure of Himmelsbach, in which the baseline was established by 30 days on placebo (12).

The results of this short-term direct addiction test confirm those of the preceding " long " addiction study, and demonstrate that continuous administration of R-1132 is associated with a low incidence of morphine-like subjective effects (reported by the patient), but with definite morphine-like changes in behaviour (rated by the aides), and is associated with the development of a moderate degree of physical dependence. Although the average daily maximum dosages attained for morphine (240 mg), codeine (1,500 mg) and R-1132 (343 mg) represent equivalent intoxicating doses (respiratory depression and/or sedation), they are not equivalent dosages from the viewpoint of suppressing morphine abstinence (figure 4), since the maximum daily dosage of morphine and codeine necessary to produce a comparable relief of the abstinence syndrome afforded by 343 mg of R-1132 would be respectively 544 mg of morphine and 2,600 mg of codeine.

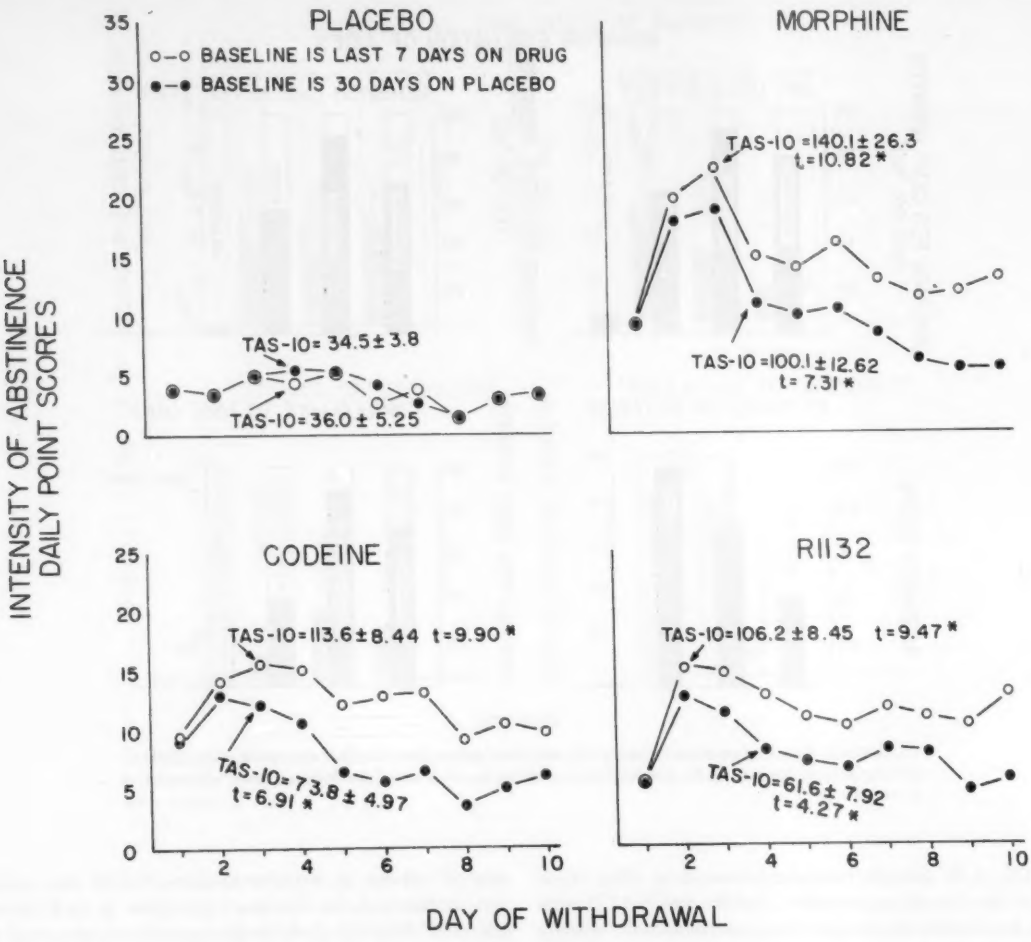

FIGURE 8

Comparative intensity of abstinence after abrupt withdrawal of morphine, codeine, R-1132, and a placebo (experiment 9). Daily point scores were computed by using the averages for rectal temperature, respiratory rate, blood pressure, and caloric intake observed during the last seven days of addiction (standard Himmelsbach method) for the baseline, and also by using the averages observed during 30 days on placebo (modified Himmelsbach procedure). The TAS-10 values represent the mean areas (total intensity of abstinence for 10 days) ± the standard error of the means. " t " values refer to the significance of the difference in the degree of abstinence observed with each drug as compared to that ascertained when the placebo was considered to be the " drug of addiction ". An asterisk indicates that the difference is highly significant.

As compared with pre-drug values, chronic administration of R-1132 did not produce any significant changes in white- or red-blood-cell counts, differential white-cell counts, hematocrit, sedimentation rates or urinalysis. There were no significant changes in body weight.

Experiment 10

" Short " direct addiction (five days) with R-1132 and codeine, using doses which were consistently " euphorogenic "

Methods. Since, in the case of drugs with low euphorogenic potency, addicts would not be likely to utilize a gradual increase in dosage, but would attempt to use doses which would provoke morphine-like euphoria, it was thought desirable in one experiment to use doses which were euphorogenic initially and to continue this dosage for five days. For comparison, not only R-1132 and codeine, but two other drugs were studied. All of these were administered orally in identically appearing capsules, and in a randomized schedule. The daily dosage was as follows: *d*-methadone (900 mg), *d*-3-methoxy-N-phenethylmorphinan (2,000 mg), R-1132 (240 mg), and codeine phosphate (480 mg). All patients received capsules four times daily, but, because of their greater length of action, *d*-methadone and R-1132 were given in only three equally divided doses rather than four.

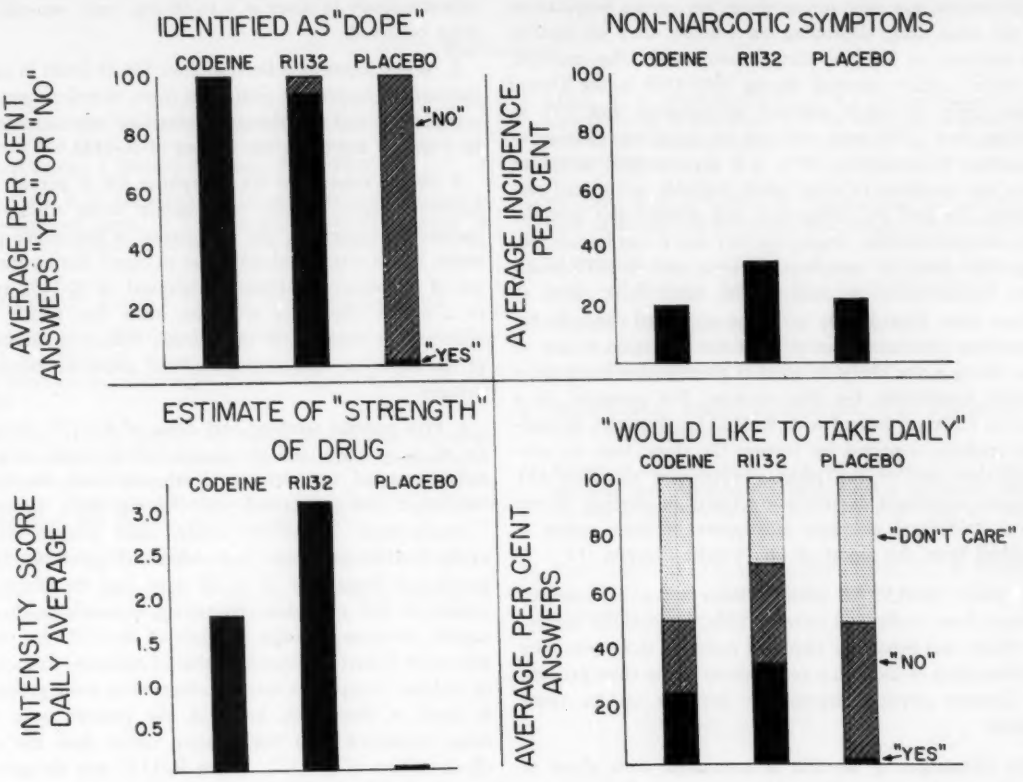

FIGURE 9

Summary of the results of patients' questionnaires in a " short " direct addiction test (experiment 10), when patients received for five successive days " euphorogenic " oral dose levels of R-1132 and codeine phosphate. These are compared with results reported after a placebo given for ten consecutive days.

The schedule provided for ten days' pre-drug observations during which placebo capsules were given on a four-per-day schedule, and then five days of medication followed by ten days on placebo until all drugs were administered. Patients were unaware of the drugs to be given or their sequence of administration, but were advised that certain of the drugs might induce toxic symptoms, and that the patient could voluntarily discontinue any drug at any time. All observers knew the complete schedule and were instructed to discontinue any medication and/or administer nalorphine promptly should any serious symptom of intoxication develop. Observations were made daily as enumerated for the " short " (18 to 20 days) direct addiction test, including the completion of " subjective " and " behavioural " questionnaires.

Results. Under these conditions the response of the patients differed greatly from that observed when the dosage was gradually accelerated. In the four subjects used, codeine was always identified as " dope", R-1132 was so identified 19 out of 20 times, and placebo was identified as " dope " once during the pre-drug period of ten days, or once in 40 times (figure 9). The incidence of non-narcotic symptoms was greater for R-1132 than for codeine, and the estimates of strength were much higher than that reported in the previous experiment. In the case of the other two drugs, toxic symptoms developed in certain patients and it was necessary to terminate the medication before the five days had been completed. It was not necessary to discontinue either codeine or R-1132 on this account. It may be concluded that when R-1132 was administered on a temporary "euphorogenic" schedule the patients' liking for the drug was comparable to that of codeine.

Discussion

Abuse liability, as pointed out by Isbell (13), depends on a multiplicity of factors and includes the quality of euphoric effects induced, the speed of onset and duration of that effect, presence or absence of side effects regarded as undesirable or desirable by the addict, ability to suppress abstinence, intensity of the abstinence syndrome at its peak after withdrawal, duration of the abstinence syndrome, and the ability to continue use of the drug either intravenously or subcutaneously. Furthermore, there are considerable variations in

addictiveness, not only among drugs but among preparations of the same drug, depending on whether they are suitable for injection or for oral administration only. For example, of 45,957 addicts reported during 1955-1959 in the United States, only 155 were addicted to paregoric and 171 to codeine, but 1,396 were addicted to morphine (Bureau of Narcotics, 30 September 1959). It is apparent that morphine has a low incidence of abuse when available as a mixed preparation for oral use (paregoric), and codeine also possesses low addiction liability despite the fact that it can be injected. Since the doses of morphine, codeine and R-1132 which were euphorogenic in these studies were from three to sixteen times those which would be employed clinically for controlling diarrhoea, it is apparent that addiction to any of these drugs is not likely to occur if given orally under strict medical supervision for this purpose. For example, in a series of 830 cases treated with R-1132 for diarrhoea of multiple etiology, reported by Janssen (3), there was no evidence that any of the patients developed morphine-like euphoria, significant degrees of tolerance, or physical dependence. Additional evidence in support of these points is furnished from the report of Dr. Vander Stappen (14).

However, R-1132 has abuse liability when administered in large doses orally and intravenously, because the subjective effects and behaviour observed resemble those seen after administration of morphine and codeine in the same patients, and because physical dependence develops on an abuse schedule.

The advantages of R-1132 as compared with those of morphine and codeine from the viewpoint of abuse may be outlined as follows: (i) R-1132 is very insoluble in water and, if compounded with inert ingredients for use as an oral preparation, addicts would be confronted with a major chemical extraction procedure if they tried to prepare an adequate amount for intravenous use; (ii) it would not be suitable for subcutaneous abuse; (iii) the onset of euphoria is slow by all routes of administration; and (iv) it induces less physical dependence than morphine, although it offers no advantage over codeine in this respect.

R-1132 exhibits greater abuse liability than *d*-propoxyphene, especially in respect to the properties of tolerance and physical dependence (9).

Summary and conclusions

1. Administration of single oral, sucutaneous, or intravenous doses of R-1132 in the therapeutic range did not induce morphine-like subjective effects or behavioural changes. However, in a dose range of from 40 to 60 mg R-1132 provoked definite morphine-like euphoria and behavioural changes by the oral and intravenous routes. When given subcutaneously in doses of 5 to 50 mg, only minimal effects were observed.

2. When substituted for morphine for 24 hours in addicted patients, it suppressed abstinence from morphine practically completely, and the dosage equivalence was considered to be 1 mg of morphine for 1.8 mg of R-1132.

3. When substituted for morphine for a period of ten successive days, R-1132 was slightly more effective than codeine in preventing the appearance of abstinence phenomena, but it was not identified as an opiate during the interval of substitution. Abrupt withdrawal of R-1132 resulted in a milder abstinence syndrome than that which occurs after abrupt withdrawal of codeine, following substitution of the latter in equivalent morphine abstinence-suppressing dosages.

4. Five patients received oral doses of R-1132 chronically for 45 to 61 days, and the dosage was gradually and carefully increased as tolerance developed until the average maximum dosage attained was 188 mg daily. In another "double-blind" cross-over study, eight patients received orally R-1132, morphine, and codeine, all given in a rapidly accelerated dosage for 18 to 20 days, and the effects were compared with a placebo. Objectively, especially on the more rapidly increasing dosage schedule of R-1132, the over-all pattern of behaviour resembled that of addiction to morphine or codeine, except that sedative effects were more prominent. In both of these tests, however, the patients were much more impressed with the sedative rather than the opiate characteristics of R-1132. When R-1132 was abruptly discontinued in both of these studies, a definite but mild abstinence syndrome developed, which was significantly less severe than that observed when oral morphine was withdrawn from the same patients, but comparable to the abstinence syndrome that ensued after abrupt withdrawal of oral codeine.

5. When R-1132 was administered chronically in high dosage, nalorphine precipitated a moderately severe abstinence syndrome.

6. When R-1132 and codeine were continuously administered in high and euphorogenic dosages at different times for five consecutive days, both drugs were identified consistently as an opiate (dope), and the effects of both drugs were liked by the patients.

It is concluded that R-1132 possesses abuse liability. Considering all the data available, it appears that this is definitely less than that of morphine and greater than that of *d*-propoxyphene. Although the abuse liability of R-1132 is comparable with that of codeine in several respects, the unsuitability of R-1132 for parenteral injection decreases the hazards that may attend its use in clinical practice.

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